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Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing

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Abstract

The brain requires a continuous supply of energy in the form of ATP, most of which is produced from glucose by oxidative phosphorylation in mitochondria, complemented by aerobic glycolysis in the cytoplasm. When glucose is limiting, ketone bodies generated in the liver and lactate derived from exercising skeletal muscle can become important compliments to glucose as energy substrates for the brain. In neurodegenerative disorders of ageing, brain glucose metabolism deteriorates in a progressive, region-specific and disease-specific manner. This brain glucose problem is best characterized in Alzheimer disease where it begins pre-symptomatically. This Review discusses the status and prospects of therapeutic strategies for countering neurodegenerative disorders of ageing by rescuing, protecting, or normalizing brain energetics. Approaches described include restoring oxidative phosphorylation and glycolysis, improving insulin sensitivity, correcting mitochondrial dysfunction, ketone-based interventions, acting via hormones that modulate cerebral energetics, RNA therapeutics, and complimentary multi-modal lifestyle changes.

[H1] Introduction

Increased longevity over the past 50 years has contributed to a rising prevalence of neurodegenerative disorders of ageing (NDAs), particularly Alzheimer disease (AD) and Parkinson disease (PD). These disorders are a major socioeconomic and medical challenge with little prospect of a solution so far. Some drugs provide a degree of symptomatic relief, but disease-modifying treatments for NDAs remain elusive despite concerted attempts to counter the pathological processes of neurotoxic protein accumulation, neuroinflammation **[G]**, axonal or synaptic dysfunction and neuronal death[1,2].

Since the concept was first reported 40 years ago, evidence has been accumulating that impaired brain energetics is involved in the aetiology and progression of NDAs, especially AD[3-7]. Brain energy metabolism declines subtly during ageing and is frequently present before diagnosis of NDA; it both drives and is driven by functional impairment and neurodegeneration in a destructive cycle[3,6].

Accordingly, a broad range 'brain energy rescue' strategies has recently been explored and is the focus of this Review. These strategies aim to impede the onset and progress of NDAs by improving, preserving and/or restoring brain energy status. We first summarize how fuel is supplied and used across various cell types in the brain, including central, peripheral and endocrine mechanisms that modulate brain energy homeostasis as well as cognitive and neuronal function. The core features of disrupted brain energetics in the five main NDAs — AD, PD, Huntington disease (HD), frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) — are then outlined. This forms the basis for a range of brain energy rescue strategies reported in preclinical and clinical studies, including promoting mitochondrial function, alternative fuel sources such as ketones **[G]**, hormonal interventions to improve insulin sensitivity and brain glucose metabolism, and complementary lifestyle approaches. Finally, we highlight genetic and other emerging approaches to enhance and restore brain energetics and we consider the challenges of translating promising preclinical results towards the dual goals of symptom relief and disease modification in NDAs.

[H1] Brain energetics

Despite representing just over 2% of adult body weight, the human brain accounts for 20% of the body's total energy requirement[8]. The brain's main competitors for energy are the liver, kidneys and heart, which have as high or higher rates of energy consumption per gram, but their overall energy consumption is lower than the brain's. The immune system also consumes considerable

energy, especially when activated in NDAs[9]. Brain energy metabolism is influenced by the endocrine modulation of appetite and whole-body energetics, processes compromised during healthy ageing and in NDAs (Supplementary Table 1)[10]. Food intake, glucose-sensing mechanisms and energy homeostasis are themselves regulated by a complex set of neural networks that in turn modulate autonomic function, appetite, reward and executive functioning. These downstream circuits are beyond the scope of this Review, and have been reviewed elsewhere[11,12].

[H2] ATP

ATP is the main currency of brain energy metabolism. Most ATP is used by Na^+/K^+-ATPase and Ca^{2+}-ATPase, the cell membrane pumps that reset ion gradients during neuronal signaling[8,13,14]. Excitatory (glutamatergic) neurons consume 80–85% of the brain's ATP, with inhibitory neurons and glial cells accounting for the remainder[15-17]. Although non-signalling pathways and cellular processes, including axonal transport, maintenance of cytoskeletal architecture, proton leakage, microglial motility, DNA repair, RNA translation and phospholipid remodelling consume less energy than neurotransmission, the energetic requirements of these processes remain hard to define[13,16]. ATP is also a neurotransmitter released from neurons, astrocytes and microglia **[G]**[18].

[H2] Glucose

Glucose accounts for ≥95% of ATP production in the brain[8]. Within the brain, glucose uptake is orchestrated across several cell types collectively known as the neurovascular unit: brain capillary endothelial cells, pericytes, astrocytes, oligodendrocytes **[G]**, microglia and neurons — the final beneficiary of glucose uptake (Figure 1)[19,20]. The normally tight spatial and temporal association of local blood flow, oxygen consumption and glucose consumption in the brain is termed neurovascular coupling **[G]**, and is the basis for functional magnetic resonance imaging[20].

Brain uptake of glucose from the circulation is driven by the energy demand of activated neurons not by the level of circulating glucose. Indeed, under normal conditions, the capacity to transport glucose into the brain exceeds the brain's energy requirement by 2–3-fold[15]. Simply put, glucose is actively 'pulled' into an area of the brain in response to increased local neuronal activity. Glucose transport is achieved by the coordinated activity of glucose transporters on the capillary endothelium (GLUT1) and plasma membrane of astrocytes (GLUT1, GLUT2, GLUT7), oligodendrocytes (GLUT1) and neurons (GLUT3 as well as GLUT4) in the cortex, hippocampus and cerebellum[10,17,21]. Only GLUT4 is mobilized as a direct response to sustained synaptic activity; its

membrane insertion is stimulated by the metabolic sensor, AMP-activated protein kinase (AMPK)[17]. Membrane translocation of GLUT4 is insulin-dependent in muscle and adipose tissue and probably also in neurons so insulin resistance **[G]**, as occurs in NDAs, is characterised by reduced neuronal glucose uptake[17,22].

To reach neurons from capillaries, blood glucose either diffuses directly through the extracellular space or is channeled through astrocytes *via* their end-feet, which surround the capillary walls. It is taken up by astrocytic GLUT1 and exits through GLUT1 on perisynaptic processes adjacent to neurons and oligodendrocytes (Figure 1). Some glucose that enters astrocytes is metabolized to ATP and some is converted to lactate, which can act both as a neurotransmitter (discussed below) and as an alternative energy source[18].

[H2] Energy use by brain cells

The ATP required by neurons is predominantly generated within mitochondria by oxidative phosphorylation **[G]** of glucose via the tricarboxylic acid cycle **[G]** (TCA cycle; also known as the citric acid or Krebs cycle; Box 1)[14]. Additional ATP is generated by aerobic glycolysis **[G]** in the cytoplasm, which is required to support the high energy demands of synaptic transmission[17]. Glutamate is the neurotransmitter in most excitatory neurons and is recycled by astrocytes and delivered back to neurons as glutamine for reconversion into glutamate or (to a lesser degree) for use in energy generation by the TCA cycle[13,23]. Compared to astrocytes, neurons favour oxidative phosphorylation over aerobic glycolysis, have more-rapid TCA cycling and contain less phosphorylated pyruvate dehydrogenase. In contrast, the energy requirements of astrocytes are predominantly met by aerobic glycolysis, so some microdomains in astrocytes contain relatively few mitochondria[23].

Neuronal activation transiently triggers aerobic glycolysis in astrocytes thereby generating lactate. The astrocyte–neuron lactate shuttle **[G]** hypothesis proposes that neuronal release of glutamate during neural transmission stimulates glucose uptake, glycogen catabolism, aerobic glycolysis and lactate production in neighboring astrocytes[8,24]. The lactate produced by astrocytes is posited to support neuroplasticity, although its precise contribution and conditions of lactate exploitation remain unclear[8,10,15,23] (Box 2).

Oligodendrocytes obtain ATP primarily by aerobic glycolysis. They use lactate for their own energy needs and also supply neighbouring axons with lactate, a process modulated locally by glutamate release from neurons (Figure 1). This metabolic support of neuronal function by

oligodendrocytes is important for effective spatial and temporal information processing in neuronal networks[25]. Oligodendrocytes are responsible for myelination of axons, which speeds up action potential conduction. However, the insulating myelin sheath restricts access of axons to glucose and other metabolites that would otherwise diffuse across the extracellular space[25]. The intermittent pattern of axonal myelination in cortical grey matter helps maintain access to extracellular nutrients[26]. Therefore, the supply of glucose and lactate to myelinated axons by oligodendrocytes requires a highly specialized architecture of the myelin sheath, including a continuum of nanometer-wide cytosolic channels that flank compacted, mature myelin[25] (Figure 1). These channels connect the oligodendrocyte soma with the periaxonal space. Interestingly, neurons also deliver *N*-acetyl-aspartate to the oligodendrocytes soma via these channels; this *N*-acetyl-aspartate (as part of the aspartate–oxaloaspartate–malate shuttle) stimulates the TCA cycle and mitochondrial ATP production and is used to generate lipids and myelin[27].

Axons also transport mitochondria, RNA, proteins, vesicles and other cargo to presynaptic terminals. This transport is an ATP-dependent process regulated by calcium and involves motor proteins and microtubules. Retrograde transport of vesicles to the cell body for lysosomal degradation is ATP-driven[2]. Fast-conducting axons release trace amounts of glutamate, which stimulates local *N*-methyl-D-aspartate (NMDA) receptors in oligodendrocytes, promoting surface expression of GLUT1 on axonal myelin sheaths and thereby increasing glucose uptake and the rate of aerobic glycolysis. This in turn increases local provision of lactate to axons for ATP generation (Figure 1)[21,28]. In addition, the molecular motors driving fast axonal transport **[G]** are equipped with glycolytic enzymes allowing them to generate their own energy "onboard"[29] (Figure 1).

Unlike astrocytes and oligodendrocytes, microglia do not directly provide energy to neurons, but the high amounts of lactate released by activated microglia may well be retrieved by local neurons[23]. Microglia are predominantly fueled by oxidative phosphorylation, but are metabolically reprogrammed by neuroinflammation in NDAs, to an aerobic-glycolysis-predominant phenotype associated with upregulation of GLUT1 and GLUT4[1,2]. In parallel with this energetic shift, microglia transition from a protective to a disease-driving role in NDAs. When brain glucose supply is chronically suboptimal, the high energy demands of activated microglia further limit energy availability to neurons[1,30].

[H2] Neuronal networks and energy use

The provision of energy substrates from astrocytes to synapses, and from oligodendrocytes to axons is critical for communication both within and between brain networks[25]. Brain regions are connected by tracts of myelinated axons, which are adversely affected by NDAs. For example, corticocortical loops are disrupted in AD and FTD, cortico-striatal pathways in HD, corticospinal tracts in ALS and nigrostriatal projections in PD. These tracts consist mainly of long-range excitatory neurons. Inhibitory interneurons, such as fast-spiking interneurons, are mostly present within local networks, such as the CA3 region of the hippocampus and frontal cortex. Local interneuron dysfunction disrupts synchronization between remote neuronal networks and across brain regions[31,32].

Gamma-oscillations (30–100 Hz) are fast brain rhythms synchronizing the activity of excitatory principal neurons and neuronal networks[31]. Fast-spiking GABAergic interneurons generating gamma oscillations have a high density of mitochondria in their axons and specialised myelination that facilitates provision of energy by oligodendrocytes[33]. The high metabolic needs of fast-spiking interneurons are supported primarily by oxidative phosphorylation. Parvalbumin-positive, GABAergic interneurons are particularly sensitive to deficits in energy and oxygen supply[13,34]. The decreased ability of oligodendrocytes to provide lactate to axons probably aggravates the decline in fast-spiking interneuron activity observed in NDAs.

Rhythmically firing, highly branched, nigrostriatal dopaminergic neurons in the substantia nigra pars compacta are especially vulnerable to mitochondrial failure and oxidative stress, features characteristic of PD (Supplementary Table 1)[13,35].

[H2] Neuroendocrine mechanisms

As demonstrated in diverse cellular and animal models, insulin has a globally positive influence on cerebral energy balance and function. It reinforces neuronal energy supply by increasing neuronal glucose uptake by GLUT4 in the hippocampus and cortex (Supplementary Table 2)[17,22]. Insulin and activation of insulin-like growth factor (IGF)-1 receptors also promote synaptic plasticity and cognitive processes[36]. Nevertheless, normal insulin sensitivity is paramount; insulin resistance is a major risk factor for AD because it disrupts both the modulation of energy availability by insulin and insulin signalling pathways in the brain[37,38].

Other hormones including ghrelin, incretins **[G]**, leptin, amylin and adiponectin modulate both appetite and energy homoeostasis and influence numerous aspects of brain function that are compromised in NDAs. The neurobiology of these hormones and their synthetic agonists in

relation to food intake and energy homeostasis, brain energy balance, mitochondrial function, cognition, motor function, neurogenesis, synaptic integrity and neuronal integrity in animal models of NDAs are documented in Supplementary Table 2, with their clinical effects reported in Tables 1-3 and in the section – Therapies based on brain energy rescue.

[H2] Brain use of ketones and lactate

Glucose (and glycogen) reserves within the brain can supply its ATP needs for only a few minutes[24,39]. Much of the brain's resilience in the face of energetic challenge therefore depends on opportunistic use of alternative fuels sourced from outside the brain. Ketones and lactate are the main alternative fuels to glucose and are delivered to the brain by monocarboxylic acid transporters **[G]** on astrocytes and on the capillary endothelium (Figure 1). The two principal ketone bodies (ketones, acetoacetate and D-β-hydroxybutyrate [BHB]), are the main alternative brain fuels to glucose in adults under conditions of dietary carbohydrate or energy restriction. In infants, however, ketones are not only an *essential* brain fuel but also the main substrate for brain lipid synthesis[40].

Acetoacetate and BHB are both in equilibrium in the blood, but only acetoacetate is metabolized to acetyl coenzyme A (acetyl CoA) which then enters the TCA cycle to generate ATP. After an overnight fast, plasma ketones are usually 0.1–0.2 mM and they supply 3–5% of brain energy requirements. However, during a 3-4 day fast, plasma ketone concentrations can reach 5–6 mM and provide ≥50% of brain energy requirements[3]. Unlike glucose, which enters the brain in response to brain cell activity, the rate of ketone entry to the brain is directly related to their plasma concentration[3], which explains the glucose-sparing effect of increased ketone levels[41]. Unlike glucose, ketones do not undergo aerobic glycolysis and cannot be metabolized to lactate, so only contribute to ATP production via oxidative phosphorylation.

[H2] The gut–brain axis

The gut microbiome is involved in bidirectional communication between the gastrointestinal tract and the brain. The intestinal microbiome generates nutrients and modulates overall energy homeostasis[42]. Disruption of the gut microbiome (dysbiosis) is implicated in the pathogenesis of NDAs[43]. Dietary fibre is an important substrate for generation of short chain fatty acids **[G]** by the gut microbiota; dietary fibre also slows down glucose absorption, which improves insulin sensitivity. These effects of dietary fibre are partly mediated by short-chain fatty acids, which are

ligands for G-protein-coupled hydroxycarboxylic acid receptors (i.e. HCAR2) in enterocytes[42,44]. Short chain fatty acids produced by gut bacteria, particularly butyrate, are key fuels for intestinal cells. Propionate, butyrate and succinate (a precursor of propionate) generated by microbiota also improve control of peripheral glucose metabolism, adiposity and body weight[44]. In pre-clinical studies, exogenous butyrate promotes the development of dendritic spines, long-term potentiation, myelination and memory formation[45]. However, butyrate levels produced endogenously are usually low so would at best be expected to be minor energy substrates for the brain.

The beneficial effect of intestinal gluconeogenesis on insulin sensitivity and systemic energy metabolism is mediated in part by glucose-sensing in the portal vein. This information is relayed via portal sensory nerves to the brain, which suppresses appetite and reduces hepatic gluconeogenesis[44,46]. Short chain fatty acids also modulate the immune system, stimulate the release of hormones such as glucagon-like peptide-1 (GLP1) from the gut (Supplementary Table 2) and inhibit histone deacetylases.

[H1] Impaired brain energetics

Impaired brain glucose metabolism compromises transmembrane ion transport, vesicle recycling and synaptic signaling[17,31,34]. Less-effective maintenance of transmembrane ion gradients and transmitter release, especially in fast-spiking interneurons, leads to hyperexcitability, excitatory/inhibitory imbalance and functional impairment of cortical networks which further compromises the brain's energy efficiency. These changes are exacerbated by disrupted glutamatergic transmission and abnormal astrocyte and oligodendrocyte function[13,34,47,48], as well as impaired autophagy which, in turn, decreases nutrient recycling[2]. Furthermore, fuelling the neuroinflammation common in NDAs is energetically expensive[1,2,49].

The pattern of brain energetic disruption depends on the NDA and its pathophysiological phenotype (Supplementary Table 1). Indeed, brain glucose hypometabolism in NDAs has no single cause; reduction in neuronal glucose uptake, impairment in aerobic glycolysis and the TCA cycle, failure of axonal transport, and the loss of glial energetic support to neurons are all implicated. Supplementary Box 1 outlines how induced pluripotent stem cells (iPSCs) and organoids are illuminating the cellular substrates of energy dysregulation, and Supplementary Box 2 summarizes how disruption of the cerebral microvasculature exacerbates the disruption of brain energy supply in NDAs.

[H2] ***Alzheimer disease***. AD is the most common NDA. It is associated with weight loss and poor appetite but also type 2 diabetes (T2D), all of which contribute to lower brain energy availability, uptake of glucose, TCA activity, mitochondrial function, astrocyte and oligodendrocyte energetic support of neurons, as well as microglial consumption of glucose due to neuroinflammation (see Supplementary Table 1)[1,4,50-52].

Even before diagnosis of AD, a characteristic regional disruption of glucose metabolism is linked to neuropathology and reduced cerebral blood flow in the brain. Nevertheless, the brain in AD still has normal or near-normal oxygen, lactate and ketone metabolism[3,52-54]. Many positron emission tomography (PET) studies confirm that the entorhinal cortex and parietal lobes including the precuneus have a 10–12% deficit in glucose uptake in mild cognitive impairment **[G]** (MCI), a deficit that becomes anatomically more widespread with the onset of AD and worsens during its progression (Box 4; Supplementary Table 1). The regional pattern of the brain glucose deficit distinguishes AD from FTD, PD, Lewy body disease and other disorders associated with dementia[3,4,6].

White matter atrophy in AD impairs neuronal network operation and axonal mitochondrial transport. Especially in women, white matter loss reflects reduced maintenance and synthesis of myelin (energy-intensive processes) and catabolism of myelin to provide energy in the face of glucose scarcity[37,55,56]. However, as with impaired glucose uptake in grey matter, white matter ketone uptake remains normal in AD[57].

[H2] ***Parkinson disease***. In idiopathic PD, weight loss and low body mass index are common despite increased visceral fat. A decline in glucose metabolism is seen in the striatum (caudate), the frontal cortex and several other cortical regions but not in the cerebellum: this hypometabolism correlates with specific patterns of motor and cognitive dysfunction and is predictive of disease progression[4,58,59]. Although PET imaging cannot resolve the substantia nigra pars compacta where dopaminergic cell bodies degenerate in PD, mitochondrial fragmentation and dysfunction including decreased glycolysis and reduced complex 1 activity, is pronounced in this brain region[50,60]. Energetic deficits have been reproduced in PD-derived iPSCs over-expressing the gene encoding α-synuclein[61]. There is evidence that neuroinflammation further compromises neuronal fuel supply in PD[1].

[H2] ***Huntington disease***. HD patients characteristically lose weight, even when increasing their calorie intake. In pre-symptomatic HD, brain glucose hypometabolism is seen the striatum, frontal and temporal cortex, and is linked to impaired neurotransmission in cortico-striatal tracts[62]. Glucose uptake, ATP generation by aerobic glycolysis, mitochondrial function and oxidative phosphorylation are all decreased in HD[35,63,64]. Astrocytes in the striatum may oxidize fatty acids as an alternative source of energy but reactive oxygen species (ROS) contribute to further tissue damage[65]. The cerebellum is less severely affected by impaired glucose metabolism than the basal ganglia, perhaps because it uses amino acids for gluconeogenesis[65]. HD neurons show disrupted glycolysis[66] and impaired axonal transport of vesicles owing to the interference of mutant huntingtin protein with molecular motors[35 67].

[H2] ***ALS and FTD***. FTD and ALS have overlapping genetic risk factors and clinical and pathophysiological features[6,68-70]. Both are characterized by increased energy expenditure, yet only in FTD is there a distinctive carbohydrate/sweetness preference and gain weight. In contrast, ALS patients lose weight eventually due to insufficient nutrient and energy intake (Supplementary Table 1)[68,71]. Brain energetics also deteriorate differently in ALS and FTD. FTD is associated with declining glucose metabolism and cerebral blood flow, especially in the frontal lobes, striatum and thalamus where mitochondrial function is disrupted with reduced signalling to the endoplasmic reticulum and aberrant mitophagy[6,68,69,72]. Conversely, ALS is associated with a regionally complex pattern of lower and higher brain glucose metabolism: of particular note are reductions in mitochondrial function and glycolysis in the cortex, spinal cord and motor neurons, and at neuromuscular junctions in muscle[68,70,73]. In the Superoxidase Dismutase 1 mouse (SOD1) model of ALS, the pentose phosphate pathway is also impaired[71]. Further, a loss of mitochondrial energetics and impaired glycolysis in astrocytes is linked to disruption of *C9orf72*, a genetic risk factor for ALS associated with failure of energetic support of neurons by astrocytes and oligodendrocytes[74,75].

[H2] Energy deficits and neurotoxic proteins

Brain glucose hypometabolism contributes to synapse loss and neuronal death in AD, with energetic deficits and neurotoxic protein accumulation mutually aggravating one another in a vicious cycle (Figure 2A)[3,52,76,77]. Insufficient neuronal glucose and mitochondrial energy generation compromise the clearance of amyloid-β (Aβ) 42 and tau proteins from the brain.

Conversely, accumulation of Aβ 42 and tau trigger mitochondrial damage, impair energy production and increase oxidative stress[77,78]. These neurotoxic proteins also inhibit GLUT4[51] and phosphofructokinase, thereby blocking glucose uptake aerobic glycolysis and ATP synthesis[79]. Mitochondria accumulate in axonal swellings and are no longer replaced in presynaptic terminals[80]. Failure to clear dysfunctional mitochondria by mitophagy further compromises the bioenergetics of vulnerable neuronal circuits in AD, PD and other NDAs[2]. Excitation/inhibition balance is crucial for network operation at optimal energetic efficicency[48] and, at the circuit level, an early, neurotoxic protein-driven feature of AD is the energetically expensive hyperexcitability of glutamatergic neurons[34,81] which is associated with an imbalance between excitation and inhibition in local cortical and hippocampal networks[32,47].

Interestingly, Aβ is involved in a healthy neuronal response to damage and/or infection[82] but this protective function is lost when Aβ aggregates into plaques. As mentioned above, Aβ exacerbates brain glucose hypometabolism, both in foci of Aβ accumulation and in remote regions, possibly due to a pericyte-mediated constriction of capillary blood flow. In turn, this hypometabolism triggers cellular damage and neuroinflammation[77,83]. Perturbed astrocytic and oligodendrocyte function, together with accumulation of phosphorylated tau (pTau), exacerbates aging[32] and Aβ/Tau-induced network hyperexcitability, thereby perpetuating a cycle of neurodegeneration and declining brain glucose metabolism (Figure 2A)[13,47]. This vicious cycle driven by energy-failure in AD has similarities with the neural circuit disruption seen in schizophrenia[84] and in epilepsy[4] and contributes not only to deterioration of memory and cognition but also to abnormal behaviour in affected patients.

[H2] Energetics and endocrine dysregulation

Insulin resistance is a common feature of AD, PD, FTD, ALS and probably also HD with reduced signalling at central insulin and IGF-1 receptors contributing to deficits in neural function, synaptic plasticity and cellular integrity (Table 1, Supplementary Table 1)[36,37,85]. Even though insulin itself does not globally promote brain glucose uptake, insulin resistance reduces glucose uptake by cortico-hippocampal neurons expressing GLUT4[17,22].

NDAs are associated with numerous changes in hormones that modulate brain energetics and neuroplasticity (Supplementary Table 2). The following observations may be highlighted: *First*, plasma leptin and hippocampal leptin signaling are reduced in AD, resulting in a state of leptin resistance mirroring insulin resistance[86]. This decline in leptin is superimposed on a background

of declining plasma leptin with ageing and is linked to impaired learning, memory and long-term potentiation[87]. *Second*, an age-related reduction in ghrelin signalling in the temporal cortex may be related to neuronal damage and cognitive deficits in AD[88]. Circulating ghrelin is reduced in PD and the loss of its neuroprotective properties is linked to dopaminergic neuron degeneration and motor dysfunction[88,89]. In addition to blunted neuroprotective properties, anti-neuroinflammatory effects of ghrelin involving astrocytes and microglia may be diminished in AD and PD[88,90]. *Third*, amylin oligomers and aggregates are suspected to damage neurons and the microvasculature in AD, though amylin has a Janus-faced role as further discussed below[91-93]. *Fourth*, an increase in circulating adiponectin has been reported in AD and ALS: if centrally expressed, this increase might counter cognitive deficits and exert neuroprotective properties but this awaits confirmation[86,94 95,96]. In contrast to the above-mentioned hormones, there are very few data on the relationship between GLP1 and glucose-dependent insulinotropic polypeptide (GIP) and NDAs (Supplementary Table 1)[97]. Brain hormone levels are challenging to measure, and cause-effect relationships hard to disentangle but changes in the secretion and central actions of these hormones are implicated in the energy imbalance, pathophysiology and functional deficits can still be inferred in NDAs (Supplementary Table 2).

[H2] Energetics and disease risk factors

[H3] ***Age***. Ageing is the main risk factor for NDAs but there is an important distinction between the cognitive, structural and neurometabolic changes associated with healthy ageing versus those occurring in NDAs. During healthy ageing, some cognitive domains such as episodic and working memory and processing speed show a modest decline, whereas others (such as semantic memory) change relatively little[98]. Although the decline in brain volume and cortical thickness forms a continuum between cognitively healthy ageing, MCI and AD, regional changes in brain glucose metabolism seen during healthy ageing are quantitatively and qualitatively different to those in MCI and AD[99,100]. In healthy ageing, the main decrease in brain glucose metabolism is in the frontal cortex, whereas in MCI and AD, the parietal lobe and precuneus are the most markedly affected [Box 4]. Decreased aerobic glycolysis[101], loss of myelination, network perturbation and attenuation of neurovascular coupling are integral features of the ageing brain that might provide a template for the onset of the more severe brain energetic deficits in NDAs[32,56,102,103]. Mitochondrial proteins are expressed at lower levels in brains of older people experiencing accelerated cognitive decline[104].

[H3] ***Metabolic dysregulation***. The risk of NDAs is substantially higher in conditions of metabolic dysregulation, including insulin resistance, obesity and T2D (Table 3)[105]. Most strikingly, poorly controlled type 1 diabetes (T1D) or T2D is associated with increased risk of cognitive impairment and AD[106]. Intriguingly, similarities exist between AD and T2D with respect to the disruptive effects of amyloidogenic proteins in the AD brain and amylin in the pancreas and brain in T2D, as well as their peripheral metabolic and vascular abnormalities[107]. In young women with polycystic ovary syndrome, mild insulin resistance is associated with a pattern of glucose-specific brain hypometabolism similar to that seen in elderly people[108], suggesting that the adverse effect of insulin resistance on brain energy metabolism is independent of age.

T2D doubles the risk of developing PD, possibly owing to increased expression of α-synuclein[85]. Interestingly, while the risk of ALS is increased in T1D, obesity and T2D are associated with decreased risk of ALS[2,74]. The metabolic syndrome associated with insulin resistance and weight gain is also present in "atypical" major depression, itself often co-morbid with NDAs, especially AD and PD[109]. Effective treatment of T2D, metabolic syndrome and depression would be expected to reduce the risk of developing AD and other NDAs[110].

Despite the chronic deficit in brain glucose uptake and utilization in, the normal ketogenic response to low plasma glucose levels is not stimulated because the main drivers of endogenous ketone production – low blood glucose and low insulin – are absent. Chronic mild hyperglycemia and mild insulin resistance commonly develop as people age, so plasma insulin rarely drop for long enough to release the insulin-mediated inhibition of lipolysis in adipose tissue, the source of the endogenous free fatty acids needed for ketogenesis. This metabolic deterioration continues as AD develops, so the brain experiences a chronic, progressive glucose-specific brain energy gap **[G]**[3] (Figure 2A) that is not corrected by ketone production as it would be if insulin sensitivity was normal and plasma glucose was decreased by a period of carbohydrate or caloric restriction **[G].**

[H3] ***Oestrogen***. Menopause is associated with deteriorating systemic and brain glucose metabolism, weight gain, insulin resistance and loss of mitochondrial efficiency[111]. Ovariectomized rodent models of menopause show metabolic responses similar to fasting, including increased oxidation of long chain fatty acids and elevated plasma ketones, as well as white matter and myelin degeneration, changes that in part reflect the use of brain lipids as a source of fatty acids for ATP generation[56,112]. In fact, oestrogen modulates many facets of brain

glucose metabolism, including uptake, aerobic glycolysis and oxidative phosphorylation[37]. Oestrogen also stimulates the catabolism and clearance of Aβ, in part by upregulating insulin-degrading enzyme, so the loss of oestrogen after menopause could directly favour pathological processes leading to AD[56,112]. Accordingly, declining plasma oestrogen is associated with increased incidence of AD in women, although this relationship remains controversial[37,112].

[H3] ***Genetic risk factors***. Possession of two *APOE-ε4* alleles (encoding the ApoE4 polymorphism of apolipoprotein E) confers the highest genetic risk of sporadic AD. In *APOE-ε4* carriers the brain is hyperexcitable[113], has reduced glucose utilization in regions affected by glucose hypometabolism in AD[114], and accumulates more aggregated Aβ. Regardless of age, the following all decline in *APOE-ε4* carriers in response to a high fat diet - brain insulin signaling[115], expression of glucose-regulating enzymes and glucose transporters[114], mitochondrial function in the cortex, and cognitive function [104,116]. These effects of ApoE4 on brain energetics are additive to the adverse effects of Aβ[77].

Some of the adverse effects of ApoE4 may result from production of a C-terminal fragment of the ApoE4 protein, which inhibits the electron transport chain **[G]**[117,118], increases generation of ROS and forces neurons to increase their reliance on aerobic glycolysis or alternative energy substrates[118]. Whether or not ApoE4 affects ketone metabolism in individuals with MCI or AD is controversial. In one AD study, a ketogenic supplement did not raise plasma ketones or improve cognitive outcomes as much in *APOE-ε4* carriers as it did in non-carriers[119]. A clinical trial of medium-chain triglycerides **[G]** in AD who were specifically selected noncarriers of *APOE-ε4* showed beneficial cognitive outcomes after 1 month[120]. However, in transgenic mice expressing human *APOE-ε4*, the presence of ApoE4 did not significantly affect brain ketone uptake versus that is wild-type controls[114].

Polymorphisms in major risk genes for PD, including *PINK1* (encoding PTEN-induced putative kinase protein 1) and *PRKN* (encoding E3 ubiquitin-protein ligase parkin) are closely linked to impaired brain ATP production[50,121]. Phosphorylation of the endocytic sorting protein Rab10 by leucine-rich repeat serine/threonine-protein kinase 2 (LRRK2) is essential for GLUT4 translocation to the neuronal plasma membrane and is defective in PD patients possessing the *LRRK2* G2019S mutation[122]. In HD, axonal transport of mitochondria and glycolytic proteins to the synapse is hindered by mutant huntingtin protein[29]. In ALS and FTD, the proteins encoded by risk genes such as *TARDBP* (encoding TAR DNA-binding protein [TDP]-43) interfere with mitochondrial function

and quality control, thereby compromising ATP production[123]. Furthermore, the most prominent risk gene for ALS and FTD, *C9orf72*, encodes part of a complex with guanine nucleotide exchange factor activity that is linked to decreased autophagic lysosome-driven nutrient recycling, leading to frontal and thalamic glucose hypometabolism and aberrant lipogenesis[2,124]. Indeed, many products of risk genes associated with NDAs interfere with autophagic lysosomal clearance which has a doubly disabling effect because the metabolic end-products of carbohydrates, fats and proteins are then lost to energy generation pathways[2].

[H1] Therapies based on brain energy rescue

As outlined above, the prevailing notion that impaired brain glucose metabolism in NDAs is simply a *consequence* of neuronal dysfunction is being re-evaluated. The progressive decline in brain glucose uptake and metabolism creates a chronic brain energy gap that contributes to brain cell dysfunction even before onset of neuropathology and symptomatic cognitive deficits[3] (Figure 2B). Once glycolysis is impaired and neuronal function starts to decline, the brain energy deficit cannot be corrected by simply increasing blood glucose; indeed, additional dietary glucose aggravates the insulin resistance already commonly present in older people[10]. Furthermore, brain glucose uptake is driven by neuronal activity not by circulating glucose level[3]. Conversely, ketones and lactate are an alternative brain energy source[41], brain uptake of which is driven by their availability in the circulation.

Because no single common pathway causes brain energy deficits in NDAs, brain energy rescue strategies may need to target different metabolic pathways and processes depending on the disease in question[3,4,125] (Figure 3B). Some of these strategies focus on a single enzyme, transporter or metabolite, but others are broader (Tables 1-3). The following discussion first addresses the energetic dimension of mitochondrial dysfunction in NDAs. Strategies that have broader effects such as modulating redox status and ketone-based approaches are described next, then hormone-based approaches to brain energy rescue, following a suite of novel strategies currently under exploration. These strategies could all act synergistically with preventive lifestyle changes, i.e. increased exercise, dietary improvements and a reduction of insulin resistance[126,127] (Table 3, Box 3). For links between mitochondrial dysfunction, oxidative stress and neurodegeneration, see two recent reviews[60,78].

[H2] Support of mitochondrial function

Despite continued uncertainty about the extent to which mitochondrial damage is a consequence versus cause of the onset or progression of NDAs[65], considerable research focuses on improving mitochondrial function by protecting the electron transport chain, promoting mitochondrial biogenesis **[G]** and/or reducing oxidative damage to mitochondria[125]. Assessment of mitochondrial integrity is mostly indirect but histochemical evidence of decreased cytochrome C activity in post-mortem brain samples from young adult *APOE-ε4* carriers[118] demonstrates that impaired mitochondrial function can be present in pre-symptomatic individuals at risk of AD.

CP2, a proprietary tricyclic pyrone, improves cognitive and behavioural phenotypes in transgenic AD mice, in part by binding to and partially inhibiting the flavin mononucleotide subunit of complex 1. This improves mitochondrial bioenergetics and overall brain energy status, possibly because of increased mitochondrial biogenesis[128]. CP2 also stimulates AMPK, promotes neuronal resistance to oxidative stress, reduces brain levels of pTau and Aβ, improves axonal trafficking, and increases brain-derived neurotrophic factor (BDNF) and synaptic proteins in vivo [128,129]. Controlling the activity of complex 1 specifically seems to underpin this beneficial effect[130] because mutations that inhibit both complexes 1 and 3 or both complexes 1 and 5 are detrimental to brain energetics[131].

The mitochondria-targeted antioxidant, Mito-Q, reduces oxidative stress in mitochondria and is neuroprotective in several NDA models (Table 1). Resveratrol stimulates mitochondrial biogenesis through the sirtuin 1 (SIRT1)/AMPK/peroxisome proliferator-activated receptor (PPAR)γ coactivator 1α (PGC1α) pathway. Resveratrol also recruits AMPK to enhance autophagy, which removes damaged organelles (including mitochondria) and misfolded proteins and recycling their components, thereby promoting ATP generation[2,132]. Replacement of old and/or damaged mitochondria starts in the neuronal cell body with new mitochondria being transported along axons to presynaptic terminals[15]. Both ageing and NDAs increase mitochondrial division in a manner decoupled from normal fission–fusion cycle, suggesting that mitochondrial fragmentation could be beneficial in NDAs[133]. Quinazolinone or its derivatives such as mitochondrial division inhibitor 1 (Mdivi-1) were originally described as selective inhibitors of mitochondrial fission, but their neuroprotective effects in both *in vitro* and *in vivo* models of AD, PD and traumatic brain injury are now thought to reflect impaired mitochondrial fusion and biogenesis[134-136], and possibly improved function of complex 1.

A pilot clinical study showed that S-equol, a selective oestrogen receptor-β agonist, improves cytochrome C oxidase activity in AD[137], so treatments that improve mitochondrial function by

selective partial inhibition of complex 1, target mitochondrial uncoupling proteins or increase mitochondrial biogenesis may result in clinical improvement in NDAs (Table 2). Mitochondrial uncoupling proteins could help cells to resist oxidative and metabolic stress[98]. Low doses of the uncoupling agent, dinitrophenol, had a neuroprotective effect in preclinical models of AD, PD and HD[138]. In a mouse model of HD, mitochondrial respiration was improved by bexarotene, a retinoid X receptor agonist and PPARδ activator[139].

[H2] Redox state, glycolysis and the TCA cycle

The redox state **[G]** of a cell is typically measured by the ratio of oxidized to reduced nicotinamide adenine dinucleotide (the NAD^+:NADH ratio), which is a non-invasive marker of global brain energy status[5,78,140]. In general, nutrients and metabolites that raise either blood NAD^+ levels or the blood NAD^+:NADH ratio improve the energetic status of the brain[141]. The NAD^+ precursor, nicotinamide riboside, mitigates cognitive impairment, synaptic degeneration and neuronal death in transgenic mouse models of AD[78,98,142]. Nicotinamide riboside also improves mitochondrial function in PD neurons and reduces age-related loss of dopaminergic neurons and associated motor deficits in an animal model of PD[143]. Another potential approach to raising the NAD^+:NADH ratio is dietary supplementation of oxaloacetate[144]. In several *in vitro* and animal models of PD, terazocin (a drug approved for benign prostatic hypertrophy) stimulated phosphoglycerate kinase-1 activity, aerobic glycolysis and ATP production[145]. Patients taking terazocin to treat other conditions had a decreased risk of developing PD and slower PD progression, so its repurposing to treat PD seems promising.

Supplementation with pyruvate could potentially improve brain energetics by stimulating pyruvate dehydrogenase[146,147], a possibility supported by the rescue of defective aerobic glycolysis by pyruvate in HD-derived hIPSC[66]. Treatments that improve mitochondrial function have had mixed success in preclinical models of ALS and these approaches remain largely untested in humans[70,74].

Interventions that raise circulating ketones also increase acetyl CoA which fuels the TCA cycle independently of aerobic glycolysis. Preclinical studies show that supplementation with BHB, caprylic acid (an 8-carbon saturated fatty acid), oxaloacetic acid, capric acid (a 10-carbon saturated fatty acid), as well as a ketogenic diet **[G]** or caloric restriction (Box 3), all contribute to increased TCA cycle activity within the brain[144,148] (Figure 3B). In humans, plasma medium-chain fatty acids increase long enough after oral ingestion to be transported into and metabolized by

the brain[149]. TCA cycle intermediates also give rise to bioactive molecules such as the neurotransmitter, acetylcholine, that are decreased in AD. These responses are generally reversible and therefore transformation of glutamate into α-ketoglutarate (which enters the TCA) generates ATP in neurons and glia[98].

Triheptanoin, a triglyceride of heptanoic acid, delays motor symptoms and is neuroprotective in animal models of ALS[74], epilepsy and ischemic stroke[150,151]. Triheptanoin also reduces the effort needed to undertake exercise in HD, a beneficial effect associated with increased creatine phosphate in the brain[152]. Triheptanoin appears to substitute for the branched-chain amino acids that are an endogenous substrate of anaplerosis **[G]** and are decreased in HD[152,153].

[H2] Ketone-based strategies

Several clinical trials show that ketogenic interventions result in cognitive and/or functional improvements in MCI[154-156], AD[119,120,157-159] and PD[160,161]. These interventions fall into two categories: ketogenic dietary supplements containing medium-chain triglycerides (either caprylic acid (C8) alone or caprylic acid plus capric acid (C8C10); and the very low carbohydrate ketogenic diet (Table 2; Box 4). In the phase 1[119] and phase 2[154] placebo-controlled studies of C8 and C8C10 supplementation, the interventions lasted from 12 weeks[119] to 6 months[154], respectively. Two subsequent feasibility studies of ketogenic diets in AD showed improved global cognitive scores in the most compliant patients but did not have control groups[157,162].

A recent 6 month study of C8C10 supplementation in MCI showed a direct and statistically significant dose–response relationship between brain uptake of ketones and/or plasma ketone and executive function, verbal fluency and language, strongly implying that ketones were directly and mechanistically linked to cognitive improvement via brain energy rescue[154]. Because of the short half-life of ketones in the body, however, the main challenge with ketogenic interventions is to achieve a sustained therapeutic level of ketosis. In two studies of ketogenic supplements that had a sample size large enough to provide adequate statistical power to assess cognitive outcomes, the 24-h average plasma ketone level was ≤0.2 mM for C8[119] and ≤0.4 mM for C8C10[154]; these ketone levels would only have partially corrected the brain energy deficit in MCI and less so in AD (Figure 2B, Box 4). In other clinical trials with a ketogenic diet in AD[157,162], MCI[155,156] or PD[160,161], higher plasma ketone were directly related to improved clinical outcomes, but sample size and patient adherence were inadequate to produce definitive evidence of a cognitive benefit.

In PD, consuming a ketogenic diet for 8 weeks led to substantial reduction in urinary problems, pain and fatigue scores versus those in a control group consuming a low-fat diet[160,161]. The ketogenic diet group also showed a trend towards improved motor scores versus the control group. Ketogenic interventions are being explored with some success in animal models of PD[163], ALS[164] and HD[165] (Table 1), but randomized, controlled clinical trials of this approach yet to be reported. A ketogenic diet promotes neurovascular function and metabolic status in mice along with a healthier profile of intestinal microbiome[166].

Studies in which a single dose of a ketogenic supplement transiently improved cognition in AD[167] and in cognitively normal older people (66 years old)[158] suggest that ketones reduce the brain energy gap by bypassing glycolysis and providing acetyl CoA to enter the TCA cycle directly (Figure 3B). This interpretation is supported by reports that mild-to-moderate ketosis lasting <4 h prevents the autonomic, cognitive and behavioural symptoms of acute insulin-induced hypoglycemia in T1D[168]. In turn, mild ketosis probably spares some glucose to be used by pathways other than glycolysis and oxidative phosphorylation[41], i.e. the pentose phosphate pathway generates NADPH and anaplerosis for the TCA cycle (Figure 3). Whether glucose-sparing is central to the therapeutic effect of ketone supplementation remains to be determined.

Metabolism of ketones in the brain not only generates fuel, but also provides an important substrate for the synthesis of brain lipids, including myelin[40]. Ketones are also substrates for post-translational protein modification and activate cell signaling[125]. The density and activation of HCAR2 is increased in the substantia nigra in PD[169] and is neuroprotective in an animal model of PD[170]. Reducing neuronal hyperexcitability by raising GABAergic tone may contribute to the efficacy of ketone supplementation in individuals with NDAs as it does in epilepsy[13,148,171].

Disease modification, i.e. retardation or reversal of neuropathology, is a crucial goal in the treatment of NDAs. Studies in transgenic AD mice show that ketones decrease Aβ deposition in the brain[172] and reduce the excitatory effect of Aβ42 on neurons[146]. These preclinical studies have been confirmed in a pilot clinical study in MCI[156], suggesting that in addition to providing an alternative brain energy substrate that bypasses the brain glucose deficit, ketogenic interventions could potentially improve cognitive outcomes in MCI and AD by slowing pathological processes resulting in Aβ accumulation.

High-fat diets are commonly perceived to increase the risk of cardiovascular disease so it is important to consider their potential risks. Very-high-fat ketogenic diets have been assessed in five clinical trials of durations ranging from 6 to 12 weeks. Three of these trials were conducted

in MCI or AD[155,157,162] and the other two in PD[160,161]. In none of these trials were common biomarkers of cardiovascular risk increased, including body weight or plasma LDL cholesterol or triglycerides. However, no standard definition of a ketogenic diet exists and some 'high-fat' diets used experimentally (and possibly also clinically) might indeed adversely affect cardiovascular health outcomes because they contain an excess of refined carbohydrate. In clinical trials, ketogenic medium-chain triglycerides were not associated with increased cardiovascular or metabolic risk (Table 2); indeed, like the very high fat ketogenic diet, medium-chain triglycerides are commonly used to treat obesity and T2D, which are risk factors for NDAs.

[H2] Increasing insulin sensitivity

Brain energy homeostasis is closely linked to peripheral insulin sensitivity, both of which depend on the balance between global energy intake and use. The two main determinants of peripheral insulin sensitivity are exercise and intake of refined carbohydrate[173]. When lifestyle changes are ineffective or difficult to implement, peripheral injections of insulin are commonly used to treat T2D, but the challenge is to avoid episodes of hypoglycemia and exacerbation of insulin resistance which increase morbidity[168].

[H3] Intranasal insulin and insulin sensitizers. Intranasal insulin and intranasal insulin sensitizers could potentially mitigate the deleterious effects of insulin resistance and a glucose deficit (Figure 3, Tables 1-3). Intranasal insulin enters the brain directly via olfactory neurons, which enables treatment of CNS insulin resistance while minimizing systemic hypoglycemia. Short-term studies show that intranasal insulin enhances cognitive function in healthy young adults, MCI and mild-moderate AD, in part by stimulating brain glucose metabnolism[38,174]. Little or no intranasally administered insulin enters the peripheral circulation but intranasal insulin delivery still needs to be optimized to achieve a more consistent increase in brain insulin before its efficacy for cognitive improvement can fully be assessed[38].

Metformin decreases hepatic glucose production which improves insulin sensitivity in T2D so it is being investigated for therapeutic use in NDAs[175]. Metformin reduces neuropathology and corrects memory deficit in AD mice[176] and normalizes cortical network disruption and anxious behaviour in HD mice[177]. Within the brain, metformin also stimulates autophagy, improves synaptic function and reduces neuroinflammation, effects that mimic those of caloric restriction and exercise[2,178]. Metformin suppresses coupling of the redox and proton transfer domains of

complex 1, but its overall mechanism of action remains unclear [179,180]. Recent data suggest that growth/differentiation factor 15 and its receptor GDNF family receptor α-like may mediate the influence of Metformin on metabolism, suggesting they could be novel therapeutic targets for safely combating brain energetic deficits associated with NDAs[181], but it may also exacerbate Aβ accumulation[182]. Indeed, Metformin is potentially protective against cognitive decline in MCI or AD[183,184] and cognitive impairment due to stroke[185]. However, adverse effects of Metformin have been linked to over-activation of AMPK and vitamin B_{12} deficiency[132], so additional studies are needed[175,186].

Impaired brain glucose uptake and insulin receptor desensitization could potentially be corrected by targeting nuclear hormone receptors that suppress neuroinflammation by activating insulin-regulated and IGF-regulated pathways. For example, thiazolidinediones are PPARγ agonists that potentially reduce brain insulin resistance associated with AD and other NDAs[36]. In contrast, PPARγ agonists, including pioglitazone and rosiglitazone, has produced no cognitive benefit in clinical trials in AD. Inhibitors of sodium–glucose co-transporter 2 such as dapagliflozin increase glucose excretion, improve cardiovascular outcomes and reduce mortality in T2D[187]. In addition, these agents induce mild ketonemia[188] suggesting that they should be tested in NDAs, perhaps in combination with ketogenic interventions.

[H3] Incretin hormones. GLP1 receptor agonists such as Liraglutide are approved to treat insulin resistance, obesity and T2D[189,190]. Based on encouraging findings in animal models of AD, PD, HD and ALS (Table 1, Supplementary Table 2), they are also being assessed for treatment of NDAs[97,191,192]. For example, Liraglutide and Exenatide reduced neuropathology, neuroinflammation and microvascular pathology and improved cognitive outcomes in a transgenic mouse model of AD (Table 2)[192]. A GLP1 receptor agonist reduced Aβ accumulation and reduced mitochondrial pro-apoptotic signaling, while increasing anti-apoptotic signaling and BDNF[192]. Semaglutide, a long-acting GLP1 analogue, was more neuroprotective than Liraglutide in an animal model of PD, a beneficial effect related to improved mitochondrial function and lower oxidative stress, apoptosis and neuroinflammation[97]. Inhibitors of GLP-1 breakdown are now in clinical trials to treat NDAs[193].

In mild-to-moderate AD, Liraglutide for 6 months attenuated the decline in brain glucose uptake but had no effect on brain Aβ load or cognitive outcomes[194]. Exenatide reduced symptoms of PD in a phase II trial[195]. Interestingly, Metformin might exert its actions partly via GLP1[36]. Some

dipeptidyl peptidase 4 (DPP4) inhibitors (gliptins) approved to treat T2D are known to prolong the activation of GLP1 [196]; one such agent, Sitagliptin, improved cognition in elderly diabetic individuals with or without AD[197].

GIP agonists have shown similar benefits to GLP1 agonists in mouse models of PD[198,199]. GIP agonists closely mimic GLP1 agonists in animal models of AD[200,201]. Dual agonists of both GLP1 and GIP were more effective in rodent models of PD than GLP1 agonists alone[200,201]. A triple agonist of GLP1, GIP and glucagon receptors had broad neuroprotective activity in a mouse model of AD[202]. Clinical data are eagerly awaited for these multitarget agents.

[H3] Ghrelin. Ghrelin is neuroprotective and improves cognition in animal models of AD, PD and HD (Supplementary Table 2)[203-205]. The beneficial effects of ghrelin involve promotion of neuronal glucose uptake, increased expression of uncoupling protein 2, improved mitochondrial function, and enhanced mitophagy[88,205]. AMPK activation in dopaminergic neurons of the substantia nigra may also contribute to the beneficial effects of ghrelin in PD: AMPK activates PGC1α to induce mitochondrial biogenesis and increase ATP production, as well as stimulating autophagy to eliminate α-synuclein[2,205,206]. Since ghrelin counters gastrointestinal dysfunction in PD, Relamorelin, a centrally-penetrant and selective agonist of the ghrelin receptor (also known as growth hormone secretagogue receptor type 1), is being assessed to treat constipation in PD and T2D. The effects of Relamorelin on motor function, neuronal survival and bioenergetics are being assessed in PD[207].

[H3] Leptin and adiponectin. Leptin promotes mitochondrial function, has neuroprotective properties and mitigates the neurotoxic effects of Aβ accumulation in animal models of AD and PD[86,87,208]. Synergistic beneficial effects on mitochondrial function have been reported for leptin in combination with PPARα agonists[209]. The risk of ALS is reduced in people with T2D, so it is interesting that knocking out the gene encoding leptin (*Lep*), which suppresses appetite in a mouse model of ALS, slowed the progression of ALS symptoms while decreasing energy expenditure and increasing in body weight[210]. This suggests that leptin antagonists should be evaluated as a potential treatment in ALS. Data on adiponectin are currently limited to mouse models of AD in which adiponectin agonists had neuroprotective properties associated with reduced loads of Aβ and pTau and improved cognitive performance, benefits that were related to increased glucose uptake in the hippocampus and, possibly, to improved insulin sensitivity[86,211].

[H3] Amylin. The status of amylin as a potential target for treating NDAs is controversial[92] because native amylin itself is amyloidogenic and aggregated amylin has pro-apoptotic and neuroinflammatory effects and may seed Aβ aggregation[91,93]. Moreover, Aβ binds to amylin receptors and its neurotoxic actions and interference with cognition were blunted by an amylin antagonist[91,212]. Nevertheless, amylin itself could have potential beneficial properties as a leptin sensitizer, including leptin resistance in AD[213]. The satiety-stimulating effects of amylin may help to control weight gain as well as improve insulin sensitivity and brain glucose metabolism; treatment with human amylin or a non-aggregating amylin analogue, Pramlintide, has shown both cognitive benefits and reductions in Aβ pathology in animal models of AD[214]. Amylin and Pramlintide also promote Aβ efflux from the brain, regulate synaptic proteins, reduce oxidative stress and inflammation and improve mitochondrial function[214,215]. Pramlintide protects against the neurotoxic and memory-disrupting actions of Aβ[91]. However, whether amylin-related mechanisms can be harnessed in the treatment of AD and other NDAs remains to be seen.

[H2] Restoration of downstream signalling

An important fate of glucose distinct from its use as an energy substrate is its utilization to generate *O-linked β-N*-acetylglucosamine (*O*-GlcNAc) which is post-translationally and reversibly added to serine and threonine residues of numerous proteins. *O*-GlcNAcylation occurs via *O*-GlcNAc transferase whereas *O*-GlcNAcase removes *O*-GlcNAc residues: both of these enzymes are therapeutically targetable in NDA[216]. *O*-GlcNAcylation is important for axonal stability and synaptic plasticity and for the local and dynamic coupling of glucose utilization to glycolysis and mitochondrial function at both pre-synaptic and post-synaptic sites[216]. In primary cell culture models of PD, *O*-GlcNAcylation of α-synuclein reduced its aggregation and toxicity[217]. In addition, in transgenic mouse models of AD, downregulation of *O*-GlcNAcylation is implicated in the production of Aβ and pTau[218]. Novel therapeutic agents that aim to restore *O*-GlcNAcylation are currently under investigation in experimental models of NDAs[216-218].

[H2] Epigenetic interventions

In addition to driving the TCA cycle, acetyl-CoA is a precursor of brain lipids and a substrate for generation of acetylcholine. Acetyl-CoA is also the source of the acetyl moiety used to acetylate several enzymes that modulate glycolysis, gluconeogenesis and the TCA cycle, tau (acetylation of

which promotes its aggregation); and histones[219]. Acetylation is a core component of histone modification, which regulates gene expression, so cellular energetics are affected by the availability of acetyl-CoA for histone acetyl transferases[220,221]. Therefore, acetyl-CoA provides a direct link between brain energy balance and the epigenetic control of gene expression, a link reinforced by other components of the TCA cycle, including the intermediates, succinate and citrate[219]. Furthermore, increased activity of the deacetylating enzyme, sirtuin 1, promotes mitochondrial function[98] and is implicated in the positive influence of the exercise-induced increase in brain lactate on cognition[222]. Specific histone deacetylases in the hippocampus may contribute to the improved resilience to stress by lactate in mice[223].

Short-chain fatty acids produced by the intestinal microbiome also influence the activity of histone deacetylases[44]. For example, BHB modulates the β–hydroxybutyrylation of histones at lysine residues, which couples metabolic status to the control of gene expression[224]. Post-translational histone modifications and DNA methylation influence bioenergetic processes that are disrupted in NDA, so pharmacological modulation of these epigenetic mechanisms could improve brain energy status in NDAs[220,221].

[H2] RNA-based and DNA-based therapies

Diverse techniques are being developed to alter the level of mRNA encoding proteins that are anomalously expressed in NDAs. These strategies could suppress neurotoxic effects or compensate for a loss of physiological function, thereby improving the energetic status of the brain. Targeting specific classes of microRNAs and long noncoding RNAs that control the translation of dysregulated glycolytic and ATP-generating mitochondrial proteins should also be feasible.

Recent clinical success with oligonucleotide-based therapies in CNS disorders such as spinal muscular atrophy[225,226], together with advances in the manipulation of oligonucleotides, such as antagomirs **[G]** and locked nucleic acids **[G]**, make this approach increasingly relevant to NDAs, even for hitherto 'undruggable' targets[227-229]. In HD, clinical trials of Antisense oligomers directed against mutant *huntingtin* mRNA are underway to prevent its interference with mitochondrial transport and function[230]. In addition, allele-specific strategies that specifically decrease mutant *huntingtin* mRNA while preserving normal *huntingtin* mRNA are under investigation. Some of these interventions use zinc finger nucleases (which act as transcription factors) whereas others rely on small molecules that promote clearance specifically of the mutant proteins[231]. Antisense

oligomers and similar approaches could also be used to target genes containing mutations that disrupt mitochondrial energetics in PD and ALS with FTD (Supplementary Table 1)[232,233].

Oligonucleotides and siRNAs that modulate pre-mRNA splicing or neutralize mRNA-directed miRNAs preferentially increase the expression of the intact allele of energy-generating genes down-regulated in NDAs[226,234]. A more direct mode of gene therapy that aims to restore abnormally low or absent gene expression is to transfer copies of the intact gene into the brain using an adeno-associated virus vector. For example, the approved gene therapy onasemnogene abeparvovec employs an adeno-associated virus vector to deliver intact *SMN1* gene copies to motor neurons to treat spinal muscular atrophy[235]. An adeno-associated virus vector loaded with the human *GLUT1* promoter injected directly into the brains of GLUT1-deficient mice led to robust GLUT1 expression in cortico-limbic regions, together with increased CSF glucose and improved motor function[236]. A similar strategy that targeted dysfunctional PGC1α helped to restore mitochondrial function in dopaminergic pathways in mouse models of PD[237].

DNA and RNA editing might also become options for the treatment of NDAs, for example, using zinc finger nucleases or CRISPR/Cas9 technologies. One specific approach to improve brain energetics in AD is the conversion of the ApoE4 isoform into ApoE3 as shown in a neuronal cell line[234,238,239]. Gene editing of *APOE* has not yet been achieved *in vivo* but progress is rapid in this field and a broad range of options for improving glucose metabolism and other abnormalities associated with AD based on neutralization of ApoE4 is being investigated[240].

Finally, mitochondrial dysfunction and other disturbances associated with HD may also be linked to excessive translation of mRNAs and overproduction of proteins resulting from inactivation of the eukaryotic translation initiation factor 4E (EIF4E) translational repressor complex. Rapamycin and other repressors of this complex or its components should therefore be assessed to restore mitochondrial energetics and integrity in NDAs[241].

[H2] Photobiomodulation therapy

Low wavelengths of light penetrate brain tissue to a considerable depth and transcranial (intracranial, intra-aural or intranasal) application of near-infrared light is under study as a treatment for various brain disorders[242,243]. The mechanisms underlying the positive effects of photobiomodulation therapy await further elucidation but increased brain perfusion, energy availability and oxygen supply have been proposed, in addition to neuronal actions implicating light-absorbing cytochrome C and increased ATP production[242-244]. The use of

photobiomodulation to improve brain energetics has received initial support from small-scale clinical trials[242,243,245], but rigorous controlled studies with larger sample sizes are needed. An alternative strategy to improve the energy status of the brain could be non-invasive light and/or auditory stimulation regimes. In a mouse model of AD, this approach improved pathology and reduced neurotoxic proteins, in part by improving neurovascular coupling and, by inference, brain energetic status[246].

[H1] Conclusions and Outlook

Impaired brain energy metabolism is now recognised in NDAs and, at least in AD, clearly precedes the onset of clinical symptoms. The metabolic defects occur at multiple levels including reduced neuronal glucose uptake, impaired glycolysis and suboptimal function of the TCA cycle, all of which adversely impact axonal transport, mitochondrial function and ATP production (Figure 3A). The multiple faces of brain glucose hypometabolism present challenges for drug development in NDAs. Indeed, in view of the multiple brain energetic pathways affected, a fundamental question is whether pharmacological approaches that target a single enzyme, receptor or protein could ever be truly clinically effective. By analogy to other multifactorial disorders associated with an increased risk of NDAs, like depression and T2D[247] where multi-modal interventions are the most effective, the same could turn out to be true for brain energetic rescue in NDAs. An example would be use of agents that simultaneously clear aggregated toxic proteins and/or suppress ROS and neuroinflammation[248,249].

The efficacy of a multi-modal approach depends on a better understanding of the cause and effect relationships between the brain glucose deficit and pathophysiological processes[1,2,103]. In any event, attempting to promote energetically expensive processes such as microglial clearance, synaptic remodeling, myelin regeneration or axonal transport seems questionable unless the brain has adequate energy resources to fuel the additional work. Therefore, optimization of brain energetics should become a core component of future clinical trials of potential therapies for NDAs, irrespective of their mechanisms of action, because unless the brain can close the brain energy gap (Figure 3), potential benefits of new medications may well be missed. Furthermore, a multi-pronged approach embracing both targeted pharmaceutical treatments and broad improvement in diet and lifestyle is emerging as a viable way to improve both prognosis and clinical symptoms of NDAs[2,5,248,250]. Insights could also be garnered by considering brain energetics in other neurological diseases (Box 5).

Preclinical studies have demonstrated that brain energy rescue can delay the onset and/or progression of NDAs at two levels – (i) by improving in neuronal integrity, synaptic plasticity and neuronal–glial interactions linked to cognitive and functional deficits, and (ii) by disease modification, at least for Metformin[176] and certain ketone-based interventions[146,172]. The benefit of ketone-based interventions in NDAs resembles that seen in other brain disorders including schizophrenia[84] and epilepsy[4,251]. It is interesting that ketones and another traditional black sheep of energy metabolism —lactate — which have complementary roles both as signaling and neuroprotective molecules in brain energetics, have much to offer in developing therapeutic strategies for brain energetic rescue strategies in NDAs[3,8,252,253]. Hormone-based interventions that modulate appetite and energy expenditure should also be able to contribute to both an early preventive influence by delaying the onset of neuropathology and symptoms and a later benefit by delaying further decline in cognitive function or other functional outcomes. Genetic, epigenetic and other novel strategies are also showing promise for improving brain energetics in NDAs.

Being able to link clinical symptomatic improvement to a clinical read-out or a measurable biomarker, i.e. imaging, metabolite or hormone[76,254], would accelerate validation of clinical effectiveness and product development. In addition, an ideal biomarker would be able to predict disease-modification by an intervention. Ketone PET imaging is a biomarker of brain energy status linked to cognitive outcomes in MCI (Box 4) but it does not demonstrate whether disease modification took place. Given the probable need for a long-term multi-modal strategy including lifestyle intervention, successful compliance and retention is ultimately likely to depend on the intervention being personalized, i.e. exercise or insulin sensitizers only for those who are insulin resistant, etc.[255].

In conclusion, just as normal neurocognitive development during infancy depends on adequate brain energy supply, the maintenance of cognitive performance and cerebral function during ageing is contingent on the brain continuing to meet its energy needs. Guaranteeing the energy status of the brain should become a cornerstone for trials attempting to delay the onset and progression of NDAs. The observations discussed herein should help us move towards this important goal.

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Competing interests

S.C.C. declares that he has consulted for and has received honoraria, test products and/or research funding from Abitec, Accera, Bulletproof, Nestlé and Servier, and is the founder of Senotec. M.J.M. declares that he is a full-time employee of Servier and has no other interests to declare. M.P.M. declares that he holds patents related to therapies targeted at decreasing oxidative damage to mitochondria. G.C. declares that she holds a patent related to compositions and methods for treating cognitive deficits using amylin and other hormones. A.E. declares that

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Table 1 | Treatments that improve brain energetics and/or function in preclinical models of neurodegenerative disorders.

Study characteristics	Primary end points: results	References
Mitochondrial function		
AD mice (3xTg) receiving MitoQ (100 μM in drinking water) for 5 months	Mitochondrial function: ↓ cognitive decline, ↓ oxidative stress, ↓ Aβ accumulation, ↓ astrogliosis, ↓ synaptic loss, ↓ caspase activation, ↓ neuropathology, ↑ mitochondrial function	256
AD mice (APP/PS1) receiving 25 mg/kg/day CP2 for 14 months	Mitochondrial function:↓ complex 1 activity, ↑ AMPK, ↑ mitochondrial bioenergetics.	128
AD mice (APP/PS1) receiving 25-250 μM AP39 in neurons in culture; 100 nM/kg body weight AP39 for 6 weeks	Brain energy status and mitochondrial function: ↑ brain ATP, protected mitochondrial DNA, ↓ ROS, ↓ brain atrophy	257
AD mice (APP/PS1) receiving 10 mg/kg or 40 mg/kg mdivi-1 by gavage for 1 month	Mitochondrial dynamics: ↓ mitochondrial fragmentation, ↓ loss of mitochondrial membrane potential, ↓ ROS, ↓ and synaptic dysfunction. ↑ ATP, ↑ learning and memory, mitochondrial function	136
AD mice (APP/PS1) receiving 400 mg/kg/day nicotinamide riboside for 10 weeks	Mitochondrial function and proteostasis: ↓ Aβ accumulation. ↑ cognitive function, ↑ oxidative phosphorylation activity	258
PD rats (hA53T-α-syn) receiving 20 mg/kg mdivi-1 by i.p. injection for 8 weeks	Mitochondrial dynamics: ↓ mitochondrial fragmentation, mitochondrial dysfunction, oxidative stress, neurodegeneration and α-syn aggregates; ↑ motor function	135
HD mice (HD R6/2 and YAC128) receiving DA1 peptides (1 mg/kg/day) via osmotic pump for 2-3 months	Mitochondrial dynamics and function: ↑ mitochondrial biogenesis and bioenergetics; ↓ inflammation and neuropathology	259
ALS mice ($SOD1^{G93A}$) receiving MitoQ (500 μM in drinking water) for 30-40 days	Mitochondrial function: ↓ nitroxidative stress, neuropathology. ↑ mitochondrial function and life span	260
SCA1 mice (*$Sca1^{154Q/2Q}$*) receiving MitoQ (500 μM in drinking water) for 16 weeks	Mitochondrial function: ↓ neuropathology, oxidative stress, DNA damage, neuronal loss. ↑ mitochondrial function	261
Seizure model (risk of AD) *In vivo* study: CD1 mice; 35 energy % C10 in regular diet. *In vitro* study: astrocytes exposed to 200 mM C8 or C10 for 10 days	Seizures: *In vivo* study: ↓ seizures after C10 but not C8; No change in glycolytic enzymes*; In vitro* study: C8 and C10 ↑ basal respiration and mitochondrial leak; ↑ ATP synthesis, antioxidant capacity by C10 but not C8	150
Insulin sensitizers		
AD mice (APP/PS1) receiving 200 mg/kg i.p. metformin for 14 days	Cognitive performance, neuropathology: ↑ cognitive performance (Morris water maze) ↓ hippocampal neuron loss, ↓ Aβ,↓ neuroinflammation	176
HD mice (Hdh150 knock-in) receiving 5 mg/ml metformin in drinking water for 3 weeks	Early network hyperactivation in visual cortex, behaviour: ↓ hyperactive neurons, ↑ normal network patterns, ↓ green fluorescent protein-hht protein synthesis, ↓ anxiolytic behaviour	177
Ketogenic molecules		
AD mice (APP/PS1) receiving 26 mg/kg/day BHB and pyruvate for 5 weeks	Brain redox status: ↑ brain nicotinamide adenine dinucleotide phosphate (reduced); ↓ network hyperactivity (epileptiform discharges)	146
AD mice (3xTgAD) receiving 125 g ketone ester/kg in diet for 8 months	Brain TCA cycle activity, mitochondrial function: BHB ↑ fivefold; 30-40% ↑ brain TCA cycle and glycolytic intermediates; ↑ mitochondrial redox potential; ↓ oxidized lipids/proteins in hippocampus	262

AD mice (Sirt3$^{+/-}$/AppPs1); receiving ketone ester added at 22% of dietary energy for 20 weeks	Neurodegeneration, neuronal network hyperexcitability: ↑ cortical SIRT3 expression, ↓ loss of GABAergic neurons, ↓ seizures and prevented death of Sirt3+/- /AppPs1 mice	263
PD mice (MPTP, 18 mg/kg four times over 2 h; 40 mg/kg, 80 mg/kg or 160 mg/kg per day BHB for 7 days	Mitochondrial function: ↑ mitochondrial respiration and ATP at Complex 2; ↓ dopamine neurodegeneration and motor deficit	264
ALS mice (SOD1-G93A) receiving 10% of calories as C8 for 10 weeks (7–17 weeks old)	Physical symptoms: Mitochondrial function ↓ spinal cord motor neuron loss, ↑ mitochondrial O_2 consumption, no change in survival	265
Nutrients and metabolites		
AD mice (Tg2576) receiving 250 mg/kg/day nicotinamide riboside for 3 months	Brain redox status, cognitive performance, ↑ cortical redox status; attenuated cognitive decline	266
AD mice (3xTgAD/Polβ$^{+/-}$) receiving 3 g/L (12 mM) nicotinamide riboside in drinking water for 6 months	Brain redox status: normalized cortical NAD+/NADH; nicotinamide riboside ↑ cognitive function and restored hippocampal synaptic plasticity	142
AD mice (treated with streptozotocin) receiving 50 mg/kg N-acetyl cysteine for 9 days	Brain glucose uptake, cognitive performance: normalized glucose uptake in hippocampus after streptozotocin; prevented spatial/non-spatial learning and memory impairment	267
ALS mice (SOD1-G93A) receiving 35% of calories as triheptanoin for 5 weeks (35–70 days old)	Physical performance, TCA cycle activity, brain glucose uptake, cognitive performance: ↑ hind limb grip strength by 2.8 weeks, ↑ time to loss of balance on rotarod, ↑ time before weight loss, ↑ TCA cycle	268

Reports shown here exclude those involving the ketogenic diet and lifestyle interventions (see Box 3); studies involving antioxidants are documented in other reviews[60]. Triheptanoin[268] is a seven-carbon triglyceride. The APP/PS1 AD mice bear the APP-Swedish mutation plus the PS1-L166P mutation. 3XTgAD mice express three mutations (APP-Swedish, PS1-M146L and tau-P301L). Abbreviations not in main text: AP39, proprietary mitochondrial-targeted H_2S donor; GSK3β, glycogen synthase kinase 3 beta; mutUNG1, mutated mitochondrial DNA repair enzyme; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SCA1, Spinocerebellar ataxia type 1; TBI, traumatic brain injury; YAC, yeast artificial chromosome.

Table 2 | Clinical trials reporting improved brain function and/or energetics in neurodegenerative disorders.

Disorder	Study details	Results and comments	References
AD	Single blind RCT of S-equol (n=15) or placebo (n=15) for 2 weeks (NCT 02142777)	Well-tolerated. More participants showed ↑ cytochrome oxidase activity on S-equol than on placebo; No cognitive change. First study of a mitochondrial intervention as a direct biomarker of mitochondrial engagement in AD.	137
Mild-moderate AD and MCI	RCT in AD (n=21) or MCI (n=39) receiving long-acting intranasal insulin (20 IU or 40 IU) or placebo for 4 months (NCT01595646)	Dose-dependent ↑ memory composite score in ApoE4^{+}. No change in functional autonomy or executive function.	38
AD	RCT of liraglutide (n=14) or placebo (n=20) for 26 weeks (NCT01469351)	No change in Aβ load or cognitive scores. ↓ Brain glucose uptake over 26 wk only on placebo. Underpowered for cognitive outcomes. Liraglutide may delay metabolic decline in brain.	194
AD or MCI	RCT (n=20) of metformin 500 mg or placebo for 8 weeks (NCT01965756)	↑ Executive function. No change in cerebral blood flow.	183
PD	RCT of exenatide 2 mg once per weekk (n=31) or placebo (n=29) for 48 weeks plus 12 week washout (NCT 01971242)	UPDRS motor subscale at 60 weeks ↑ 1.0 points on drug and ↓ by 2.1 points on placebo ↓ motor symptoms.	97
AD	Double-blind RCT of C8 20 g per day (n=77) or placebo (n=63) for 90 days (NCT00142805)	ADAS-Cog ↑ by 3.4 points in ApoE4^{-}. Cognitive score varied directly as Ketones ↑ cognition in mild-to-moderate AD.	119
Mild-moderate AD	Open label (n=10) receiving KD ± C8C10 for 12 weeks (NCT03690193)	↑ ADAS-Cog score; no cardiovascular safety or other metabolic concerns. First reported clinical use of ketogenic diet in AD including medium chain triglyceride supplementation.	157
AD and MCI	RCT of KD (n=9) or NIA low-fat diet (n=5) for 12 weeks (NCT02521818)	↑ Composite cognitive score, particularly memory domain, only in compliant participants and only on KD. First reported clinical use of a KD without medium chain triglyceride supplementation. Feasibility is very challenging but beneficial effects of ketones are clearly present.	162
Mild-moderate AD	Open label study of C8C10 (n=11) or C8 (n=6) 30 g per day for 4 weeks (NCT02709356)	↑ ketones 2-fold. Brain ketone uptake ↑ in direct proportion to ↑ ketone and brain glucose utilization. In AD, the brain can utilize additional ketones provided as C8C10.	269
Mild-to-moderate ApoE4^{-} AD	Crossover RCT of MCT 17.3g (n=24) or placebo [canola] (n=25) for 30 days (ChiCTRIOR6009737)	2.62 point improvement on ADAS-Cog (Chinese version) on MCT, 2.57 worsening on placebo. Study restricted to ApoE4(–) patients. Inverse correlation between cognitive changes and plasma lysophosphatidylcholine species.	120
PD	RCT of KD (n=20) or low-fat diet (n=20) for 8 weeks (ACTRN 12617000027314)	↑ UPDRS in both groups, but 41% more on the KD. 86% compliance; tremor ± rigidity intermittently ↑ on KD. First RCT of KD in PD. KD and low-fat diets are safe in PD.	160
HD	Open label study in HD (n=10) and CTL (n=13) receiving triheptanoin 1 g/kg for 1 month (NCT01696708)	MRS ↑ brain high-energy phosphates including ↓ inorganic phosphate/phosphocreatine during visual stimulation	270

These studies reported statistically significant improvements in primary or secondary endpoints with novel treatments or drugs approved for other indications and repurposed for treatment of

neurodegenerative disorders of ageing. The low-fat diet[162] diet was a modified Atkins diet. The three KD trials were all principally feasibility studies not powered for cognitive or metabolic outcomes[157,160,162]. Abbreviations not in main text: ADAS-Cog, Alzheimer Disease Assessment Scale - Cognitive Subscale; AHAD – American Heart Association diet; ALSFRS-R, ALS functional rating scale –revised; MMKD – modified Mediterranean ketogenic diet; MRS – magnetic resonance spectroscopy; NIA, National Institutes of Aging; OAA, oxaloacetic acid; RCT, randomized controlled trial; SMC – subjective memory complaints; UPDRS; Unified Parkinson disease rating scale.

Table 3 | Clinical trials reporting improved brain function and/or energetics in major risk conditions for neurodegenerative disorders of ageing.

Disorder	Study details	Results and comments	References
T2D ± cognitive impairment	Open label (n=205) DPP4I (sitagliptin) 100 mg per day ± metformin ± insulin (n=101) vs metformin ± insulin only (n=104) for 6 months	↑ MMSE on DPP4I; similar glycemic control in both groups; ↓ insulin on DPP4I arm; RCT needed.	197
MCI or mild AD (non-diabetic)	Placebo-controlled, parallel-group cross-over study (n=10 per group) of metformin, 2 g per day for 8 weeks (NCT01965756)	CSFβ, pTau; CBF; ADAS-Cog and CANTAB® cognitive batteries: metformin measurable in CSF; no change in CSF Aβ42, pTau; ↑ CBF in two brain regions at 8 wk; trend to ↑ executive function, memory and attention. Metformin penetrates brain; underpowered for cognitive outcomes.	186
MCI	RCT of high carbohydrate (n=11) or high fat KD (n=12) for 6 weeks (NCT00777010)	Feasibility study; Cognitive outcomes (executive function, long-term memory), mood: on KD, ↑ memory (paired associate learning); no change in executive function or depression score. Metabolic improvement on KD: ↓ weight, waist circumference, fasting glucose, fasting insulin.	155
MCI	RCT of C8C10 30 g per day (n=19) or energy-matched non-ketogenic placebo (n=20) for 6 months (NCT02551419)	Brain glucose and ketone status: ↑ Brain ketone uptake 2-fold. ↑ executive function, episodic memory, language and processing speed. Several cognitive outcomes improved in direct proportion to [ketone] and/or brain ketone uptake.	154
SMC and MCI	Cross-over RCT with 6 week washout in between 6 weeks of AHAD and 6 weeks of MMKD interventions, in patients wiht SMC (n=11) or MCI (n=9) (NCT2984540)	CSF AD markers, neuroimaging markers, peripheral metabolic status, cognition: In MMKD only: ↑ CSF Ab42, ↓ CSF tau, ↑ brain ketone ↑ brain perfusion. In both groups: ↑ metabolic markers, ↑ memory. Compliance ≥90% in both groups; MMKD feasible, acceptable and has prevention effect on AD CSF biomarkers.	156

Abbreviations no tin main text: ADAS-Cog, Alzheimer Disease Assessment Scale - Cognitive Subscale; AHAD – American Heart Association diet; ALSFRS-R, ALS functional rating scale –revised; MMKD – modified Mediterranean ketogenic diet; MMSE, Mini-mental state examination; MRS – magnetic resonance spectroscopy; OAA, oxaloacetic acid; RCT, randomized controlled trial; SMC – subjective memory complaints; UPDRS; Unified Parkinson disease rating scale.

Box 1 | Generating ATP in the brain

Glucose entering brain cells is phosphorylated to glucose-6-phospate and then enters one of two pathways[14]: generation of ATP via aerobic glycolysis and the mitochondrial tricarboxylic acid (TCA) cycle or the pentose phosphate pathway which generates riboses, nucleic acids and NADPH for antioxidant defence and anabolic reactions (Figures 1, 3). The final step in aerobic glycolysis is generation of pyruvate, converted either to acetyl-CoA via pyruvate dehydrogenase for entry into the TCA cycle or to lactate via lactate dehydrogenase (Figures 1, 3). The acetyl CoA pathway predominates in neurons and the lactate pathway in astrocytes, but this is not an absolute distinction. The TCA cycle takes place in the mitochondrial matrix, with oxidative phosphorylation in the inner mitochondrial membrane. Several TCA cycle steps generate NADH and flavin adenine dinucleotide hydride, which are oxidized and donate high-energy electrons to the mitochondrial electron transport chain, which in turn drives conversion of ADP to ATP by oxidative phosphorylation. More than 90% of brain ATP is generated in mitochondria by oxidative phosphorylation. Each molecule of glucose consumed during oxidative phosphorylation generates about 33 ATP molecules[271], compared to 2 molecules of ATP produced by aerobic glycolysis. However, oxidative phosphorylation is slower than aerobic glycolysis and occurs at the price of generating ROS[60].

The TCA cycle not only feeds the mitochondrial electron transport chain but also provides carbon for synthesis of glutamate and acetylcholine, a process called cataplerosis **[G]**. Carbon exiting the TCA cycle needs to be replaced in order to maintain TCA cycle activity, a process called anaplerosis. Via pyruvate, glucose is an important contributor to anaplerosis, such that when brain glucose uptake is impaired, not only ATP production but also anaplerosis are both adversely affected. Pyruvate carboxylase generates oxaloacetate, mostly in astrocytes but also oligodendrocytes[27]. Certain branched chain amino acids and odd-chain fatty acids (such as heptanoate) are anaplerotic[272]. Ketones can replace glucose as a source of acetyl CoA but they are not anaplerotic.

The astrocyte–neuron lactate shuttle hypothesis postulates that activated glutamatergic neurons stimulate astrocytes to increase their supply of lactate to neurons[8]. Astrocytes release lactate through the low affinity perisynaptic monocarboxylic acid transporters (MCTs) 1 and 4[18]. Lactate it is taken up by high-affinity neuronal MCT2 and transformed into ATP in neurons by oxidative phosphorylation (Figure 1). ATP produced by metabolism of glucose or glycogen to lactate does not require oxygen, so this route reduces net brain oxygen consumption in cells or

organelles with a high level of aerobic glycolysis, such as hippocampal synapses[15]. Lactate derived from glycogen in astrocytes can stimulate neuronal plasticity and learning, but this effect may only occur at relatively high plasma lactates (2–5 mM)[8]. Moreover, some types of neurons, including inhibitory GABAergic interneurons, do not necessarily depend on lactate[8]. Hence, the functional importance of the astrocyte–lactate shuttle *in vivo* requires additional study[15,273,274].

Lactate may act as a paracrine regulator through the lactate receptor, hydroxyl carboxylic acid receptor (HCAR) 1 (also known as GPR81). During intense exercise, plasma lactate increases and lactate enters the brain through MCTs at the blood–brain barrier (Figure 3), activating HCAR1 and promoting angiogenesis in the hippocampus and neocortex[252,253]. Exogenously administered lactate enhances hippocampal synaptic plasticity, neurogenesis and memory formation in rodents[8].

Box 2 | Measuring brain energy metabolism

In vitro models

To measure brain high energy phosphates, fresh mitochondria are fixed and visualized by electron microscopy, and adenine nucleotides are measured by high-performance liquid chromatography. Frozen mitochondria can be used to evaluate antioxidants, oxidative damage and the activity of respiratory chain complexes. Frozen brain homogenates are used to determine the activity of glycolytic, tricarboxylic acid (TCA) cycle and electron transport chain complexes, and markers of mitochondrial biogenesis, dynamics and autophagy.

Regulatory mechanisms of energy homeostasis can be studied in single neurons and glia using nanosensors based on fluorescence resonance energy transfer which detects changes in intracellular concentrations of cyclic AMP, protein kinase A, glucose and lactate in response to activation of G-protein coupled receptors[275]. Intact brain cell respiration can be studied using an extracellular flux analyzer to establish rates of oxygen consumption, glycolysis, proton leakage, mitochondrial reserve and other bioenergetic parameters[129]. The use of reprogrammed human cells and brain organoids for advancing bioenergetic drug discovery is considered in Supplementary Box 1.

Fluorescence lifetime imaging microscopy of cells or brain slices measures mitochondrial NADH production in real time and reveals a role for astrocytes in the glycolytic deficits of a mouse model of HD expressing mutant huntingtin[65]. This technique identifies defective glycolysis as leading to mitochondrial dysfunction in AD neurons and supports the potential of pyruvate to bypass impaired glycolysis and maintain mitochondrial respiration[147]. The energetics of neuronal network activity can also be studied in cortical slices[34]. Gamma oscillations have high energy expenditure[34], in which pyruvate and BHB can partially replace glucose[276].

Brain imaging in vivo

In living organisms, brain energy metabolism is usually evaluated by positron emission tomography (PET) in which the glucose analogue, deoxyglucose, is labelled with ^{18}F to make ^{18}F-fluorodeoxyglucose (FDG). To quantify brain uptake of FDG (or ketones or oxygen) by PET, i.e. cerebral metabolic rate **[G]** (μmol/100 g/min), blood samples to measure the tracer must be obtained as near to the brain as possible. Cerebral metabolic rates obtained by PET reflect values obtained by arteriovenous difference across the brain[3], but PET provides a visual image of both global and regional brain energy metabolism. A new PET tracer of mitochondrial complex 1

function, ^{18}F-2-tert-butyl-4-chloro-5-2H pyridazin-3-one[277], has been proposed as a marker of mitochondria-specific energy failure arising before the onset of impaired glycolysis in AD, and could be used to validate new therapeutics aiming to correct mitochondrial function.

In healthy ageing individuals, the brain glucose deficit (energy gap; Figure 3) is about 8% and occurs mostly in the frontal cortex whereas in AD the parietal and temporal lobes are most deeply affected[269]. A glucose-specific brain energy deficit is also present in young adults with insulin resistance[278]. Indeed, FDG uptake might be a better marker of declining cognitive function in MCI and AD than the Aβ–PET marker, ^{18}F-florbetapir[279].

Metabolism of multiple energy substrates has been assessed in humans and animals by in vivo ^{13}C-magnetic resonance spectroscopy, including brain uptake of ^{13}C-labeled glucose and ketones[280], medium chain fatty acids[153], and non-invasive assessment of mitochondrial redox status in the rat[281].

Box 3 | Complimentary multi-modal lifestyle strategies

Lifestyle interventions may delay the onset of NDAs, as exemplified by the 'Finger' trial which reduced the risk of AD in a typical elderly population[126,250]. Two lifestyle approaches that improve brain energetics and insulin sensitivity are garnering considerable attention: caloric restriction (and the variant - intermittent fasting)[5] and physical exercise[127]. Both approaches are neuroprotective and improve cognitive and motor function in pre-clinical models of AD and PD by increasing synaptic spine density[98], mitochondrial biogenesis[282], neurogenesis in the hippocampus, autophagy of neurotoxic proteins, mitophagy of dysfunctional mitochondria[98,283], and activation of ghrelin signalling[206]. Nutritional ketosis is a feature common to caloric restriction, intermittent fasting and other ketogenic interventions[3,98,284].

Exercise helps regulate glucose metabolism and reduces two important risk factors for NDAs: obesity and T2D. Exercise also improves executive function, attention and processing speed in NDAs, effects related to enhanced cerebral blood perfusion notably in the hippocampal dentate gyrus. Exercise increases angiogenesis in several brain regions[253] and mitigates the age- and NDA-related decline in cerebral blood flow[98] which, in turn, may improve synaptic function by providing ketones and lactate[5,98,285,286]. A three-month exercise regimen increased brain ketone transport by 30% in AD[108], so the improvement in brain energetics by ketones is one possible link between exercise, BDNF, neurogenesis and cognitive gains in NDAs[286].

The angiogenic effect of exercise is partly mediated by vascular endothelial growth factor[252,253]. Lactate liberated from skeletal muscle during exercise can also be used by the brain[5,286] (Box 1). Exogenous lactate mimicked exercise in inducing brain vascular endothelial growth factor and increasing capillary density, actions dependent on hydroxycarboxylic acid 1 (HCAR1) receptors[253]. The hippocampal myokine, irisin, may also be involved; both irisin and its precursor, fibronectin domain 5, contribute to metabolic homeostasis and neuroprotection[286]. Lactate recruitment of BDNF is dependent on fibronectin domain 5, thereby interlinking the actions of lactate to irisin in the beneficial effect of exercise on the brain[222,286,287].

The goal of mimicking the gains of exercise and fasting in a broadly accessible manner by an appropriate pharmacological intervention (exercise in a pill) is analogous to using lactate[252] or a ketogenic supplement to mimic and/or augment endogenous ketone production without severely limiting dietary carbohydrate or food intake[156,157]. Exercise mimetics could include agents acting via myokines, cathepsin B, AMPK or adiponectin[98,132,286,288].

Cognitive reserve is the capacity or resilience of the ageing brain to resist functional decline and is directly correlated with higher education and intellectual occupation both early and later in life. Whether improved cognitive reserve can stall AD is currently under exploration[289]. FDG-PET suggests that cognitive reserve reflects in part the capacity of the brain to maintain normal function in the face of bioenergetic or other deficits[290,291]. Maintaining and improving cognitive reserve in individuals with NDAs could potentially be enhanced by the brain energy rescue strategies discussed herein.

Box 4 | Deteriorating brain glucose but not brain ketone uptake: an opportunity for brain energy rescue

The decline in brain glucose metabolism associated with NDAs has traditionally been assumed to be a *consequence* of the disease process. The development of PET tracers for assessing ketone uptake (Box 2) provided an opportunity to assess whether brain ketone metabolism was also disrupted. Dual-tracer PET studies of brain glucose (^{18}F-FDG tracer) and ketone (^{11}C-acetoacetate tracer) uptake show that whereas brain glucose utilization is impaired, brain ketone metabolism is still normal in AD and MCI (see figure, panel **a**). These PET images show the rate constant (min^{-1}) for brain glucose uptake (K_{Glc}; left) and brain acetoacetate uptake (K_{AcAc}; right) in cognitively healthy, older controls (CTL, n=24), mild cognitive impairment (MCI; n=20) and mild-moderate AD (n=19). The images are paired, i.e. one for FDG and one for ^{11}C-acetoacetate obtained from each participant on the same afternoon. Unlike the cerebral metabolic rate (CMR), which is partly dependent on plasma concentrations of the substrate in question, the rate constant (*K)* for uptake of ketones is largely independent of plasma levels of glucose or ketones, so it is a better measure of the brain's *capacity* to take up these energy substrates. *K* (glucose) is significantly lower in the parietal and temporal cortex as MCI develops and progresses to AD, but *K* (acetoacetate) does not decrease in MCI or AD compared to cognitively unimpaired age-matched controls[292]. The CMR of acetoacetate increases in direct proportion to plasma ketone levels in AD after one month of receiving a supplement of 30 g per day of a ketogenic medium chain triglyceride (C8C10 or C8; see figure, panel **b**). However, there was no change in the CMR of glucose[269].

Mitochondrial oxidative phosphorylation is the only way of generating ATP from ketones, i.e. there is no extra-mitochondrial pathway for ketones as there is for glucose to lactate. Accordingly, the fact that brain ketone metabolism is normal in MCI and AD indirectly implies that mitochondrial respiration is relatively normal in a significant proportion of brain mitochondria in order for them to be able to generate ATP. Hence, comparisons of brain glucose and brain ketone metabolism offer an opportunity to determine whether mitochondrial function is markedly impaired (in which case both glucose and ketone metabolism would be decreased, regionally or globally) or whether the defect is more at the level of glycolysis or glucose transport (in which case glucose but not ketone metabolism would be impaired). This PET comparison of brain energy substrate uptake could help to clarify whether the onset of mitochondrial dysfunction is an early event in NDAs, whether such dysfunction occurs in the brain regions most affected[65], and whether

a therapeutic agent being tested corrects the dysfunction or promotes mitochondrial biogenesis or other aspects of mitochondrial health.

BOX 5 | Brain energy rescue in other CNS disorders.

Owing to the success of "combined anti-retroviral therapy", patients infected with human immunodeficiency virus-1 are living longer. However, reflecting persistent neurological sequelae of the virus, about half of them develop cognitive deficits involving impaired glucose metabolism, mitochondrial dysfunction and reduced glial support of neurons. Brain energy rescue therefore might be useful to treat cognitive decline in these patients[293]. Prions are infectious particles that *lack* DNA or RNA and, in Creutzfeldt–Jacob disease, brain glucose hypometabolism is seen in frontal and parietal regions and is related to sensory and motor dysfunction[294]. Lower brain perfusion and mitochondrial dysfunction are also observed[102]. Mouse models of prion diseases mimic clinical cases in displaying altered metabolism of glucose and fatty acids[295]. Interestingly, by binding to oligomeric Aβ, prion antagonists suppress synaptic pathology and cognitive deficits in mouse models of AD, underpinning the pertinence of prion disorders to NDAs[296].

Both ischemic stroke (caused by blood vessel occlusion) and haemorrhagic stroke (caused by blood vessel rupture) involve an abrupt interruption of the supply of energy and oxygen to neurons, triggering neurodegeneration, acute brain energetic failure and functional deficits. Stroke management is driven by the twin goals of restoring blood flow and protecting mitochondrial function[60,297] in which brain energetic rescue with ketones is being assessed[298].

Like stroke, traumatic brain injury is associated not only with tissue damage but also with focal interruption of brain nutrient and energy supply. Strategies to restore mitochondrial function are under investigation in traumatic brain injury[299]. Clinical and pre-clinical studies suggest that ketogenic interventions might be therapeutically beneficial[140,300]. Furthermore, hypertonic sodium lactate reduces intracranial pressure and compensates for the acute neuronal energetic crisis in traumatic brain injury[301].

Inherited GLUT1 deficiencies (de Vivo disease) are associated with neurodevelopmental delay, motor symptoms and seizures during infancy[302]. Seizures consume considerable energy, and adult-onset epilepsy is characterized by focal brain hypometabolism, decreased glucose uptake, defective TCA cycling and mitochondrial dysfunction[34,298]. Seizures also occur with greater frequency in AD, so drugs that reinforce the GABAergic inhibition of hyperactive (energetically costly) networks[47] warrant assessment in AD. In MCI, task-induced hyperexcitability in the temporal lobe responded favourably to levetiracetam[303], an anti-epileptic drug that promotes vesicular release of GABA. In a mouse model of AD that overexpresses amyloid precursor protein, the addition of pyruvate and BHB to the diet reduced neuronal hyperexcitation and the incidence

of epileptiform activity[146]. Ketone-based interventions are also under study as a treatment for seizure-related disorders in adults because ketogenic diets are a well-established therapy for treating de Vivo disease and intractable epilepsy in children[4,251,302].

Glucose metabolism and the function of mitochondria and GABAergic interneurons are all impaired in the cortex, basal ganglia and other brain structures in schizophrenia[34,227,304]. As in epilepsy, ketone-based interventions have been proposed as a treatment for schizophrenia[305,306] and have shown encouraging results in two clinical case reports[307]. Migraine is a highly debilitating and widespread form of headache. Energy deficits and/or excessive oxidative stress within the brain are attracting attention as possible triggers and, hence, as targets for metabolically focused therapeutic interventions[308].

Finally, the retina is an outpost of the brain, and considerable progress has been made in understanding and potentially treating energetic disorders of the eye, such as age-related macular degeneration[309] (see also Supplementary Box 3).

FIGURE LEGENDS

Figure 1 | Energy supply and use by neurons and other brain cells. **a** | Overview of the neurovascular unit. **b** | Astrocytes provide energy to neurons and oligodendrocytes as lactate (Lac) via aerobic glycolysis (AG), but they also use mitochondrial oxidative phosphorylation. Astrocytes can also synthetize and store glycogen. Astrocytes take up glutamate (Glu) released from synapses and convert it to glutamine (Gln), which is sent back to neurons. Some Glu and Gln contribute carbon to the tricarboxylic acid cycle (TCA) by anaplerosis via α-ketoglutarate (αKG). Astrocytes also generate ketones from acetyl coenzyme A (AcCoA). **c** | Oligodendrocytes insulate axons with myelin and deliver lactate to axons which is transformed into pyruvate and then ATP by mitochondria. Axons promote their own energy supply by releasing Glu to stimulate NMDA receptors on oligodendrocytes. In addition to the energetic support provided by oligodendrocytes, axonal transport is aided by ATP produced locally. **d** | Microglial energy needs are mainly met by glucose but possibly also, under certain conditions, by free fatty acids and glutamine. They support neurons by clearing pathogens, waste and toxic proteins. **e** | Short chain fatty acids (SCFA) from gut microbiota and triglycerides (TG) from adipose tissue and food are transformed by the liver into ketones (β-hydroxybutyrate [BHB] and acetoacetate [AcAc]). See Supplementary Figure 1 for metabolite flow across the neurovascular unit in more detail. Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAAT, excitatory amino acid transporter; FABP, fatty acid binding protein; LDH1 – lactate dehydrogenase 1; LPL, lipoprotein lipase; MCT, monocarboxylate transporter; MGluR, metabotropic receptor; NAA, N-acetyl-aspartate; PPP, pentose phosphate pathway; Rib5P, ribonucleoside 5 phosphate; SLC, solute carrier; SNAT, sodium-coupled neutral amino acid transporter.

Figure 2 | Causes and consequences of the brain energy gap in neurodegenerative disorders. **a** | Brain glucose hypometabolism occurs in conditions that increase the risk of AD. The chronic brain energy gap and the neuropathological processes (dashed red arrow) both contribute to a vicious cycle leading to brain energy exhaustion and dysfunction. Brain energy rescue strategies (Figure 3, Tables 1-3) attempt to inhibit the positive feedback between the brain energy gap and neuropathology involving Aβ and pTau. Hormones (principally insulin, adipokines, incretins, synthetic agonists and insulin sensitizers) influence brain energy rescue and inhibit the onset of neuropathology. **b** | Glucose contributes to about 95% of total brain fuel supply ( ) in cognitively healthy young adults (HY), and ketones supply the remaining 5% ( ). In cognitively

healthy older adults (HO), brain glucose uptake is decreased by about 9%, in MCI by about 12% and in mild-moderate by about 18%. The magnitude of the brain energy gap is the difference in total brain fuel uptake (glucose and ketones combined) between HY and mild-to-moderate AD, i.e. the therapeutic target for brain energy rescue in MCI and AD. The brain energy gap has not been rigorously quantified in NDAs other than AD.

Figure 3 | Brain energy disruption and rescue strategies. a | Several pathways of brain energy metabolism in the neuron are disrupted in NDAs (dashed black arrows with disorders in red). Increased ROS production and neuroinflammation negatively impacting on brain energy levels are shown with a thick black arrow. The combination of impaired ATP production and increased ROS contribute to declining brain function. **b** | Molecules or treatments implicated in brain energy rescue strategies target six broad pathways: **ATP and redox state**, **brain glucose transport and/or aerobic glycolysis** (* intra-nasal insulin, adiponectin, ghrelin, insulin [GLUT4 only], nicotinamide riboside, dichloroacetate, N-acetyl-cysteine, oxaloacetate, GLP-1, GIP, leptin, amylin, Metformin, Liguride, Sitagliptin), **anaplerosis and the TCA cycle** (C3, C7, C8, BHB, KE), **mitochondrial transport and biogenesis**, **ketogenesis** (** BHB, C8, C10, KE) or protection against **ROS and inflammation** (*** ghrelin, GLP-1, GIP, leptin, adiponectin, Metformin, AP-39, mdivi-1, mitoQ, BHB, KD and ketone esters). Details of the molecules or treatments are in Table 1 (pre-clinical studies) and Tables 2 and 3 (clinical studies). Complementary interventions are not shown (caloric restriction, ketogenic diet, exercise). Neurons take up lactate generated by astrocytes and oligodendrocytes (not shown). MCFAs such as decanoic and octanoic acid in the circulation can enter astrocytes and produce ketones and acetyl CoA. Abbreviations: ANA – anaplerosis, ATP Syn – ATP synthase, C3 – propionic acid, ETC – electron transport chain; MCT – monocarboxylate transporter, PPP – pentose phosphate pathway.

Glossary

Neuroinflammation

An inflammatory response or state in the brain that involves functional, morphological and energetic shifts in microglia and "reactive" astrocytes, as well as macrophages that migrate into the brain from the periphery. Characteristic of neurodegenerative disorders and brain response to infectious agents or injury.

Ketone bodies

(Ketones), β-Hydroxybutyrate and acetoacetate. Produced by fatty acid β–oxidation during caloric or severe carbohydrate restriction, and from medium chain fatty acids. Exogenous ketones are mostly salts or esters of β-hydroxybutyrate. Acetone is a breakdown product of acetoacetate measurable in plasma and on breath.

Microglia

Resident brain macrophages of mesodermal origin that clear neurotoxic proteins and protect neurons from damaging exogenous molecules, toxins, infectious agents or pathogens. Excess and persistent microglial activation is associated with neuroinflammation, energetic shifts and progression of neurodegenerative diseases of ageing.

Oligodendrocytes

Cells producing myelin to insulate the axon and increase the speed of action potential propagation. Energetically support and communicate with neurons and astrocytes.

Neurovascular coupling

Coordinated response to brain activation involving local capillary dilation and a transitory surge in the flow of oxygenated, glucose-containing blood across the neurovascular unit (Fig 1), thereby replenishing ATP used in neurotransmission.

Insulin resistance

Insulin that is ineffective in stimulating glucose use by peripheral tissues and certain populations of neurons in the brain due mainly to receptor-signalling desensitization. Associated with

glucose intolerance and type 2 diabetes. Increases risk of neurodegenerative disorders, particularly Alzheimer disease.

Oxidative phosphorylation

Process by which mitochondria generate ATP by conveying electrons through enzyme complexes (I to IV), thereby creating a proton gradient that powers phosphorylation of ADP to ATP by ATP synthase (see Box 1).

Tricarboxylic acid cycle

(TCA cycle) Process by which acetyl CoA is oxidized to form GTP, $FADH_2$ and NADH. NADH and $FADH_2$ feed electrons to the electron transport chain to produce ATP by oxidative phosphorylation. Several neurotransmitters (acetylcholine, glutamate, GABA) are produced by carbon leaving the TCA cycle.

Aerobic glycolysis

Conversion of glucose to pyruvate by the "Emden-Meyerhoff pathway". Pyruvate is either converted to acetyl-CoA and enters the TCA cycle or is reduced to lactate by NADH, a pathway prominent in glia to produce ATP without oxygen. May also occur in neurons.

Astrocyte–neuron lactate shuttle

Hypothesis that lactate produced in astrocytes is delivered to neurons to support the energy requirements of neurotransmission.

Fast axonal transport

Rapid transport of vesicles, mitochondria and other cargo along axonal microtubules. Vesicles are equipped with molecular motors (kinesin and dynein) and glycolytic enzymes permitting rapid, local ATP production by aerobic glycolysis.

Incretins

Peptide hormones produced by small intestine that stimulate pancreatic insulin secretion, regulate glucose metabolism and influence cognition. Include glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide.

Monocarboxylic acid transporters

Transporters in the cell membrane that facilitate unidirectional, proton-linked transport (uptake) of small monocarboxylic acids such as lactate and ketones.

Short chain fatty acids

Acetate (2 carbons), propionate (3 carbons), and butyrate (4 carbons). End-products of microbial fermentation of dietary polysaccharides (soluble fiber). Butyrate is ketogenic and propionate is anaplerotic.

Mild cognitive impairment

(MCI) Condition prodromal to Alzheimer disease characterized by a subjective memory complaint and modest, deficits in at least one of the five main cognitive domains (executive function, memory, language, processing speed or attention). About 50% of cases progress to Alzheimer disease within 5 years.

Caloric restriction

Limiting food intake to a level that does not permit full satiety. Can be self-determined (usually the case in human studies) or imposed relative to the food consumed by a matched group fed *ad libitum* (usually only in animal studies).

Electron transport chain

A series of enzymatic protein complexes in the inner mitochondrial membrane that transfer electrons donated from NADH (complex 1) or fatty acid dehydrogenase (complex 2) to oxygen (complex 4).

Medium chain triglycerides

Edible oils comprised of saturated fatty acids of 6-14 carbons in length. Long been used in clinical nutrition to support energy needs in diseases or conditions involving malabsorption. Eight carbon medium chain triglycerides are more ketogenic than those of 10 or 12 carbons.

Mitochondrial biogenesis

Renewal of mitochondria. In neurons, mitochondrial biogenesis occurs in the cell body with newly formed mitochondria being transported along the axon to synaptic dendrites.

Redox state

Capacity of a molecule to be 'reduced' or acquire electrons. Opposite of oxidation. Many biological reactions involve the reduction of one molecular species while another is being simultaneously oxidized. Energy metabolism is highly dependent on the redox state of the cell.

Ketogenic diet

A very low carbohydrate, very high fat diet inciting the liver to produce ketones from free fatty acids because there is minimal insulin production. The stricter, medical form of the ketogenic diet developed to treat intractable epilepsy usually also limits dietary protein.

Anaplerosis

Process by which 4 or 5 carbon units enter the TCA cycle independently of acetyl CoA to replenish intermediates used in the synthesis of acetylcholine or lipids (from citrate) or amino acids (from alpha-ketoglutarate and oxaloacetate). Opposite of cataplerosis.

Brain energy gap

Deficit in brain energy metabolism on the order of 10% in mild cognitive impairment, and 18-20% in Alzheimer disease. Also present in other NDA. Appears to be specific to glucose, i.e. currently no studies have shown that brain ketone metabolism is affected.

Antagomirs

Also known as anti-microRNAs or blockmirs. Synthetic oligonucleotides engineered to silence endogenous microRNAs or prevent other molecules from binding to a specific mRNA.

Locked nucleic acids

RNAs in which the flexibility of the ribose ring has been restrained by adding a methylene bridge connecting the 2´oxygen and 4´ carbon. Oligonucleotides containing locked nucleic acids have improved specificity, sensitivity and hybridization stability.

Cataplerosis

Process by which intermediates (carbon) leave the TCA cycle to support biochemical reactions, i.e. acetylcholine and lipid synthesis from citrate, or amino acid synthesis from α ketoglutarate and oxaloacetate. Opposite of anaplerosis.

Cerebral metabolic rate

Quantity of energy substrate consumed by the brain (μmol/100 g/min). Typically refers to glucose but also used for brain consumption of oxygen, lactate and ketones.

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